Non-thyroid autoantibodies in autoimmune thyroid disease

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Autoimmune thyroid disease is frequently accompanied by other organ-specific and non-organ-specific diseases, most likely because there is sharing of genetic and possibly environmental susceptibility factors. These associations are well recognized in the autoimmune polyglandular syndromes; autoimmune thyroid disease is one of the three major endocrinopathies in the type 2 syndrome and occurs in around 4% of type 1 patients. This review considers the frequency of disease-specific autoantibodies in patients with thyroid autoimmunity and briefly examines the role of such antibodies in performing screening for the associated conditions. Recommendations are made for using such autoantibody tests in the setting of patients with autoimmune thyroid disorders, and also for the utility of screening for thyroid autoimmunity in patients with pernicious anaemia, Addison’s disease, coeliac disease, primary biliary cirrhosis, myasthenia gravis, lymphocytic hypophysitis, systemic lupus erythematosus and rheumatoid arthritis. At present, however, there are no large-scale trials that have shown the cost–benefit ratio of autoantibody screening for autoimmunity screening, and clinicians must use individual judgement combined with heightened awareness to identify who to test.

Key words: autoimmune hypothyroidism; Graves’ disease; autoantibodies; pernicious anaemia; Addison’s disease; coeliac disease; primary biliary cirrhosis; myasthenia gravis; lymphocytic hypophysitis; systemic lupus erythematosus; rheumatoid arthritis.

In any medical textbook chapter on autoimmune thyroid disease, there will inevitably be a list of conditions which are more frequently detected in such patients than would be expected by chance. Typically, the list comprises most of the other organ-specific autoimmune disorders (with notable exceptions such as multiple sclerosis, despite the higher than expected prevalence of autoimmune thyroid disease in the first-degree relatives of such patients). A varying number of non-organ-specific conditions usually figure in such lists as well, and there is generally a statement that such associations

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reflect common genetic and possibly environmental susceptibility factors at work, in concert with additional disease-specific factors that determine the clinical pattern. Such associations are most pronounced in the autoimmune polyglandular syndromes (APS). The type 1 syndrome is an autosomal recessive condition, now identified as being caused by mutations in the AIRE (autoimmune regulator) gene which encodes a transcription coactivator responsible for ensuring thymic presentation of autoantigens during development, in a way that normally allows autoreactive T cells to become tolerized. Only around 4% of such patients develop autoimmune thyroid disease, and this is never the first manifestation of the syndrome.² APS type 2 is much more common and is usually defined as the presence of two of the following disorders: Addison’s disease, autoimmune thyroid disease and type 1 diabetes mellitus; however, some have reserved the name for those with Addison’s disease plus one of the other two components.³ Typical features are show in Table 1.

Patients, and often family members, with one of these syndromes are usually aware of the possibility that there is an increased risk of additional autoimmune problems and often ask for screening tests. It is far less clear whether there are any benefits in screening for other autoimmune disorders in patients with apparently isolated autoimmune hypothyroidism or Graves’ disease. This clinical uncertainty is compounded by the commonplace observation that many such patients continue to have complaints despite the restoration of the euthyroid state, raising the anxiety that a subtle, coincident autoimmune disease may be present.

The aim of this review is to focus on the frequency of non-thyroid autoantibodies in patients with autoimmune thyroid disease (Table 2), and at the same time to provide a brief analysis of the utility of such autoantibodies as markers on an underlying disorder. It is based on a literature search performed using PubMed and keywords ‘autoimmune thyroid disease’ and either the associated disease or autoantibody. Diabetes and the related autoantibodies are considered in Chapters 7 and 8 and will not be dealt with here. Many papers describe isolated cases or families with multiple autoimmune diseases, or report disease associations rather autoantibody data. Moreover, the length of this review is such that it cannot include more than a small fraction of all the available studies; priority has been given to reviews of older studies and those studies which are large, recent, and have used appropriate control groups, as these have utilized the most contemporary autoantibody assays. Because autoimmune thyroid disease is so common compared to many of the other associated disorders (Table 2), the most informative studies are often those focussing on the associated disease rather than

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>1 in 20 000</th>
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<tbody>
<tr>
<td>Inheritance</td>
<td>Autosomal dominant; variable penetrance; strong association with HLA-B8, DR3</td>
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<tr>
<td>Female:male ratio</td>
<td>3:1</td>
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<tr>
<td>Peak age of onset</td>
<td>30–40 years</td>
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<tr>
<td>Key endocrinopathies</td>
<td>Autoimmune thyroid disease (75%)</td>
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<td></td>
<td>Type 1 diabetes (55%)</td>
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<td></td>
<td>Addison’s disease (45%)</td>
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<td></td>
<td>Vitiligo (20%)</td>
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<td></td>
<td>Alopecia areata (6%)</td>
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<td></td>
<td>Pernicious anaemia (5%)</td>
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a series of patients with thyroid autoimmunity. However, it is not always clear how such patients are recruited, and biases may creep in which could alter the frequency of thyroid autoimmunity compared to an unselected series.

Any recommendations made for clinical practice reflect these limitations. At present there is no consensus on who to screen for associated autoimmune disease or at what frequency. Equally important, there has been no cost–benefit analysis of testing for autoantibodies in patients with autoimmune thyroid disease; in the end any increased testing in one area of practice will diminish the resource available in another area.

### PARIETAL CELL (PC) AND INTRINSIC FACTOR (IF) ANTIBODIES

#### Diagnostic use

These antibodies are markers for pernicious anaemia, which is characterized by vitamin B$_{12}$ deficiency, autoimmune chronic gastritis affecting the fundus and body but not the antrum of the stomach, and a progressive course that may last 20–30 years. In one survey of people over 60 years old, the prevalence of undiagnosed pernicious anaemia was 1.9%, although those of Latin, American or Asian origin are less commonly affected. The frequency of pernicious anaemia is twice as high in women. Gastric parietal cells (PCs), which are not present in the antral region, as well as the intrinsic factor (IF) they produce, are lost in pernicious anaemia. The gastric H$^+$/K$^+$-ATPase is the target autoantigen in the PC. This enzyme provokes the production of autoantibodies which can fix complement in vitro but as with thyroid peroxidase (TPO) autoantibodies in autoimmune thyroid disease, there is still uncertainty as to any pathogenic role such antibodies play. In murine models of pernicious anaemia the key pathogenic agents are H$^+$/K$^+$-ATPase-specific CD4$^+$ T cells. PC antibodies are found in 70–95% of patients with pernicious anaemia and 30–60% of those with only atrophic gastritis. They also occur in around 30% of non-anaemic first-degree relatives of patients with pernicious anaemia.

There are two classes of antibodies against IF: blocking (or type I) antibodies recognize the vitamin B$_{12}$ binding site of IF, thereby preventing the transport of the vitamin from the stomach to its absorption site in the terminal ileum, and binding

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<thead>
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<th>Table 2. Population prevalence and autoantibody patterns in diseases associated with autoimmune thyroid disease.</th>
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<td><strong>Prevalence (%)</strong></td>
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<tr>
<td>Pernicious anaemia</td>
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<td>Addison’s disease</td>
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<td>Lymphocytic hypophysitis</td>
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<td>Systemic lupus erythematosus</td>
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<td>Rheumatoid arthritis</td>
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<td>Primary biliary cirrhosis</td>
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<td>Coeliac disease</td>
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<td>Myasthenia gravis</td>
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(or type II) antibodies which do not interfere with vitamin $B_{12}$ transport. They are found in around 70 (type I) and 34% (type II) of patients with pernicious anaemia (use of new assays may increase the frequency of type II antibodies) but they are rare in autoimmune gastritis without accompanying pernicious anaemia, therefore making them specific but insensitive markers of disease.\(^8\)

It will be seen that neither PC nor IF antibodies are sufficiently sensitive or specific for diagnosis of those with pernicious anaemia. When vitamin $B_{12}$-deficiency is suspected in general clinical practice, vitamin $B_{12}$-measurement is the most logical first step, supported by other biochemical tests such as raised homocysteine or methylmalonic acid levels: GP and IF antibodies provide ancillary information, whereas gastroscopy provides both diagnostic and causal information.

**Association with autoimmune thyroid disease**

In a review of three series of patients with Graves’ disease ($n=1333$ in total), dating from 1962 to 1971, the prevalence of pernicious anaemia ranged from 1.7 to 2.3%, compared to 4.2–12.3% in three series of 490 patients with Hashimoto’s thyroiditis and autoimmune hypothyroidism.\(^8\) These figures exceed by more than 10-fold the weighted prevalence figure for pernicious anaemia in the USA in 1996, which was estimated to be 0.15%,\(^9\) and the closely matching figure of 0.13% in the UK derived from an extensive literature review.\(^1\) The prevalence of IF antibodies in the Graves’ group ranged from 2.6 to 4.7% and was from 5.0 to 6.7% in the Hashimoto and autoimmune hypothyroidism patients; PC antibodies were measured in only two studies and were found in 22% of Graves’ and 32% of Hashimoto patients.\(^8\) In 54 women with postpartum thyroiditis, PC antibodies were found in a third during pregnancy, rising 2- to 9-fold in 10 of the 18 in the postpartum period.\(^10\) Two of the antibody-positive women developed pernicious anaemia during a 5-year follow-up.

Three recent series have added new insights. In 62 sequential patients with autoimmune thyroid disease (10 with Graves’ disease, 47 with Hashimoto’s thyroiditis, and five with atrophic thyroiditis), 35% ($n=22$) had hypergastrinaemia, in all of whom atrophic gastritis was confirmed at biopsy: 10 of these 22 also had pernicious anaemia.\(^11\) PC antibodies were found in 40% of the entire group, but these comprised only 15 (68%) of the 22 with atrophic gastritis; the remaining 10 PC-antibody-positive patients had normal gastroscopy and histology. Only seven of 22 patients with atrophic gastritis had simultaneous atrophic gastritis, pernicious anaemia and PC antibodies. In the second series, 63 randomly selected patients concordant for both type 1 diabetes and autoimmune thyroid disease were screened for pernicious anaemia using measurement of serum vitamin $B_{12}$. One patient had already had this diagnosis made, and three further asymptomatic patients were found, all of whom were IF-antibody-positive.\(^12\) Although this prevalence of pernicious anaemia (6.3%) was suggested to be higher than that in type 1 diabetes alone (around 4%), the lack of a contemporary control group makes this difficult to evaluate fully. However, in 497 type 1 diabetes patients, PC antibodies were found in 20.9% (of whom 10.5% had pernicious anaemia), increasing with age, and TPO antibodies were found in significantly more of the PC-antibody-positive subset, 33.6 versus 22.4% in the PC-antibody-negative group, supporting the increased strength of association in the presence of thyroid autoimmunity.\(^13\)

Looked at the other way, autoimmune thyroid disease is particularly common in pernicious anaemia; for example, in 22 such patients, 50% had TPO antibodies and 13.6% had thyroglobulin antibodies, 2–3 times higher than in matched controls.\(^14\)
These results support the idea that screening patients with pernicious anaemia for thyroid autoimmunity is probably worthwhile. It is also likely that those with type 1 diabetes mellitus and thyroid autoimmune disease are at increased risk of pernicious anaemia, and screening might be worth considering, although there is as yet no clear evidence that treatment of subclinical disease is beneficial, nor is it clear whether measuring PC antibodies, gastrin or vitamin B₁₂ is the best initial test. The low specificity of PC antibodies and the low sensitivity of IF antibodies mean that neither are good tools to screen for pernicious anaemia in cases of isolated autoimmune thyroid disease; vigilance, especially in the elderly or those with an anaemia, leading to appropriate testing in those with clinical symptoms, is probably the best policy.

ADRENAL ANTIBODIES

Diagnostic use

This topic is fully covered in Chapter 6 and therefore only a brief summary is provided here. The key autoantigen for antibodies in Addison’s disease is the adrenal-specific cytochrome 21-hydroxylase (21-OH); some patients also have autoantibodies against side-chain cleavage enzyme or 17α-hydroxylase, but these are most frequent in patients with APS type I and correspond to the cross-reactive steroid cell autoantibodies detected by immunofluorescence. Concordance rates of only 80% have been reported, but provided care is taken with technique, immunofluorescence methods to demonstrate the presence of adrenal cortex-specific autoantibodies can give equivalent results to immunoprecipitation assays using recombinant 21-OH. Using either method, around 80% of patients with autoimmune Addison’s disease have detectable antibodies, whereas those with non-autoimmune Addison’s diseases are antibody-negative.

Subclinical Addison’s disease is characterized by the presence of adrenal cortex or 21-OH antibodies without biochemical evidence of adrenal failure. Such a situation most commonly arises when patients with an organ-specific autoimmune disorder are tested for adrenal antibodies. Of 19 such patients studied using the cortisol response to CRH to assess subtle adrenal dysfunction, eight had an impaired response and two developed adrenal failure within 1 year. Thus, the measurement of adrenal or 21-OH antibodies provides a very useful test to determine the aetiology of primary adrenal failure, and the presence of these antibodies in organ-specific autoimmunity predicts a significant risk of developing Addison’s disease. Those with the highest antibody levels are at the greatest risk of progression. Autoimmune Addison’s disease may occur in the absence of adrenal autoantibodies, and not all adrenal antibody-positive individuals progress to overt disease, although once found to have such antibodies, annual follow-up is indicated to assess adrenal reserve.

Association with autoimmune thyroid disease

An early survey of 88 children with autoimmune thyroid disease found that 2.3% had adrenal cortex antibodies, compared to none of 117 controls. More recently, a huge series of 4353 adult patients with autoimmune thyroid disease was reported, and although the individual thyroid disorders were not specified, 1.0% had adrenal cortex antibodies and 0.1% steroid cell antibodies. Twenty three patients with Graves’ disease and 18 patients with Hashimoto’s thyroiditis who had adrenal cortex antibodies...
were available for follow-up. All but two of these also had 21-OH antibodies. Four of the Graves’ patients and two with Hashimoto’s thyroiditis (one with additional type 1 diabetes) developed overt Addison’s disease within 1.5–6 years. These results, and those in other patients with various organ-specific autoimmune diseases, indicate that adrenal cortex/21-OH antibodies are markers of a significant (but modest) risk of progression to clinical Addison’s disease, although longer-term follow-up is clearly indicated to assess life-long risk, and children with thyroid autoimmunity may have a higher risk than adults of developing adrenal antibodies.

Looked at the other way, patients with autoimmune Addison’s disease have a high prevalence of thyroid autoantibodies and autoimmune thyroid disease. A case ascertainment survey in the UK of 81 patients found that 20 (25%) had primary hypothyroidism and nine (11%) had Graves’ disease. Similar figures were reported in 125 patients from Poland, where 15 (12%) had thyrotoxicosis, 17 (14%) hypothyroidism and six (5%) subclinical hypothyroidism. In 61 Norwegian Addison’s patients without a previous history of clinical thyroid disease, seven (11%) had TPO and/or TG antibodies.

There is little doubt from these figures that annual screening of patients with autoimmune Addison’s disease for autoimmune thyroid disease is worthwhile. There is no evidence to identify the best strategy. I perform TPO antibody measurement on all newly diagnosed patients to assess future risk, advising those who are antibody-positive with normal TSH levels about symptoms of thyroid disease and the relation of this to pregnancy. Thereafter, I advise all patients to have an annual measurement of TSH. On the other hand, there is little to support routine screening of patients with autoimmune thyroid disease for Addison’s disease or to measure adrenal cortex/21-OH antibodies in this setting. Suggestive clinical symptoms of course warrant follow up; the rather slow tempo of disease evolution is somewhat reassuring in those at highest risk, although of course Addison’s disease remains a life-threatening condition.

PITUITARY ANTIBODIES

Diagnostic use

Lymphocytic hypophysitis is a rare condition, almost certainly autoimmune in origin, in which the pituitary is infiltrated by lymphocytes and transient or permanent hypopituitarism results. By 2003 over 200 cases had been reported, but it remains difficult to diagnose, and we have no clear picture yet of the entire spectrum of disease or how representative these cases are, as few centres have any extensive experience. Attempts to find autoantibodies were prompted by the need to prove the putative autoimmune aetiology and to provide a tool that might spare patients biopsy, which has been the definitive diagnostic method to date. Variable results have been reported using complement consumption and immunofluorescence assays. Apart from isolated ACTH deficiency, in which antibodies are directed against a secretory granular protein which is neither POMC or ACTH, the autoantigens involved have remained elusive, hampering efforts to define the diagnostic utility of antibody testing.

Immunoblotting studies have revealed that autoantibodies reactive with a 49 kDa pituitary protein could be detected in seven of 10 patients with biopsy-proven lymphocytic hypophysitis, but were also present in five of 52 healthy controls. Microsequencing subsequently demonstrated that the protein was the ubiquitous
The demonstration of α-enolase antibodies (by immunoblotting) in 12 (63%) of 19 patients with Sheehan’s syndrome certainly proves that these antibodies are not specific markers for lymphocytic hypophysitis, and their sensitivity and utility in the diagnostic evaluation of this condition is similarly equivocal.

Association with autoimmune thyroid disease

One of the indications that lymphocytic hypophysitis is an autoimmune disease is its association with other known autoimmune disorders including thyroid disease. In one series of 25 patients with the probably separate condition of isolated ACTH deficiency, hypothyroidism occurred in 14 (56%) and Graves’ disease in four (16%). The occurrence of autoimmune pituitary disease in autoimmune thyroid disease is inevitably rare, even if probably higher than expected. Antibodies to α-enolase were detected in four (19%) of 21 patients with Hashimoto’s thyroiditis and one (8%) of 12 Graves’ patients, compared to 10% of controls. However, using immunofluorescence to detect pituitary antibodies, 12 (20%) of 59 patients with Graves’ disease and 22 (28%) of 80 patients with Hashimoto’s thyroiditis were positive, and four of the Hashimoto group with the highest antibody levels had isolated growth hormone deficiency. These striking findings have not yet been replicated, and it is premature to recommend such antibody testing until there has been replication and the development of robust assays, following autoantigen identification.

ANTINUCLEAR (AN) ANTIBODIES

Primarily a diagnostic marker for systemic lupus erythematosus (SLE), the measurement of AN antibodies is primarily a tool for rheumatologists rather than endocrinologists, and the reader is referred elsewhere for guidelines on the use of this test. Suffice it to say here that the introduction of the human Hep-2 cell line as a routine substrate for measuring AN antibodies, instead of the heterogeneous tissues and cells used previously, has improved sensitivity and reduced uncertainty in the interpretation of this test. Nonetheless, low-titre AN antibodies are a frequent finding in subjects without significant rheumatological disease and their frequency increases with age, leading to the stark statement that AN antibodies should not be tested in patients without clinical evidence of a rheumatological disorder.

Association with autoimmune thyroid disease

The increased prevalence of autoimmune thyroiditis in SLE is compelling evidence that the organ/non-organ-specific dichotomy of autoimmune diseases is more apparent than real. At least one reason for this association is that both disorders share HLA-DR3 as a susceptibility factor. In one series, 21 (51%) of 41 SLE patients had TPO and/or TG antibodies compared to 11 (27%) of 41 controls, and twice as many SLE patients had subclinical hypothyroidism. Similar figures for subclinical hypothyroidism have been reported subsequently, with thyroid antibodies appearing, as expected, more frequently in older patients. In another series of 300 SLE patients that had no matched controls, 5.7% had hypothyroidism, but only 1.7% had hyperthyroidism, the latter probably being only slightly in excess of the expected value. Such data support
the view that patients with SLE should be examined for thyroid disease and that intermittent screening is may be warranted.

However, there is no evidence to support the use of AN antibody testing in thyroid patients without suggestive features of a rheumatological disorder, given the frequent occurrence of these non-specific markers. For instance, AN antibodies were found in 26% of 50 patients with autoimmune thyroid disease, compared to 8% of 100 controls, and the prevalence of antibodies to smooth muscle and single-stranded DNA was also increased. However, none of these patients had antibodies to the more disease-specific autoantigens, namely double-stranded DNA, extractable nuclear antigen, SS-A or SS-B. Others have also found an increased frequency of AN antibodies, but heavily dependent on assay method, in Graves’ disease and Hashimoto’s thyroiditis, and also not associated with rheumatological disease. Cardiolipin antibodies, found in the primary antiphospholipid syndrome as well as SLE, are another example of such non-specific markers, in one series occurring in 55% of patients with autoimmune thyroid disease. Recently, it has been suggested that AN antibodies are more frequent in autoimmune hypothyroidism caused by atrophic thyroiditis rather than Hashimoto’s thyroiditis; these interesting findings require confirmation in a larger cohort of patients.

RHEUMATOID FACTOR (RF)

Diagnostic use

RF is an autoantibody that binds to the Fc portion of IgG and is found in around 80% of patients with rheumatoid arthritis (RA), particularly in those with the most aggressive disease. Rheumatoid factor (RF) is potentially pathogenic but only one of many such autoantibodies in RA; antibodies against citrulline-containing proteins may be more disease-specific, having negative predictive values of 75% and positive predictive values of up to 100%. However, normally measured RF is relatively non-specific and insensitive as a diagnostic or predictive tool: RF occurs in the presence of immune complex disorders, such as bacterial endocarditis, and in response to large concentrations of recall antigens. B cells from healthy individuals can be induced to produce low-affinity RF by Epstein–Barr (EB) virus transformation, and around 5% of healthy individuals have RF, a percentage that increases with age. As with AN antibodies, the recommendation is that RF should not be tested for in the absence of any features of a rheumatological disease.

Association with autoimmune thyroid disease

Several series have reported an increased frequency of autoimmune thyroid disease in RA. For instance, in a series of 58 multicase UK families with RA, 6% of the patients had thyroid disease, and 5% of the men and 15% of the women had TPO antibodies. In a controlled series of 101 RA patients from Greece, 12.9% had TPO antibodies, compared to 8.6% of controls, and similar findings have been made in Norway and Quebec. A recent series of 25 RA patients from Brazil found that 32% had TG and/or TPO antibodies compared to 4% of 113 controls, although in a similar series of 64 UK patients, the frequency of TPO antibodies was only 11%. Overall, these data support an association between RA and autoimmune thyroid disease, which is probably
not as strong as the association of the latter with SLE. Indeed, it seems likely that
reports of an association between polymorphisms of the \textit{CTLA-4} gene and RA have been
confounded by the association between RA and autoimmune thyroid disease strongly
linked to this polymorphism.\textsuperscript{50}

Given the high prevalence of RA in the general population (Table 2), it is debatable
whether screening for autoimmune thyroid disease is warranted; screening with TSH
levels alone may be inadequate, especially in patients taking corticosteroids.\textsuperscript{51} At the
least, this association should be borne in mind in patients with RA who have new
symptoms. On the other hand, the poor predictive value of RF antibodies does not
justify their use in routine screening of patients with autoimmune thyroid disease.

\textbf{ANTIMITOCHONDRIAL (AM) ANTIBODIES}

\textbf{Diagnostic use}

AM antibodies react with the E2 components of the 2-oxo-acid dehydrogenase
complexes in mitochondria, especially the E1\textsubscript{a} component of the pyruvate
dehydrogenase complex, and are present in most patients with primary biliary
cirrhosis (PBC).\textsuperscript{52} There is no evidence for a pathogenic role for AM antibodies. The
prevalence of PBC has probably been underestimated, and the condition is found in
around 0.01\% of the population, especially women aged over 40.\textsuperscript{53} AM antibodies can
be detected long before clinical disease develops, and their presence is strongly
associated with progression to PBC. They are relatively disease-specific, although only a
third of unselected patients with AM antibodies will actually have PBC at the time of
detection.\textsuperscript{54}

Up to 15\% of PBC patients may be consistently AM antibody-negative, and even
more if standard immunofluorescence assays are used.\textsuperscript{55} Thus, the detection of AM
antibodies, particularly by immunoblotting or enzyme-linked immunosorbent assay
(ELISA), is a rather sensitive and specific marker for established PBC or a strong risk of
developing this disorder.

\textbf{Association with autoimmune thyroid disease}

Uncontrolled studies have shown an excess of autoimmune thyroid disease in PBC; for
instance, 13 (22\%) of 58 patients with PBC had hypothyroidism in one series, 34\% had
TPO antibodies and 20\% TG antibodies.\textsuperscript{56} More recently, the frequency of unspecified
clinical autoimmune thyroid disease was reported to be 21\% in 200 PBC patients, and
34\% had thyroid autoantibodies; unlike RA, this study also showed that \textit{CTLA-4}
polymorphisms were associated with PBC in the absence of autoimmune thyroid
disease.\textsuperscript{57}

In 351 sera selected for TPO antibody positivity, AM antibodies were found in seven
(2\%), six of whom were asymptomatic and four had normal liver function tests.\textsuperscript{58} This
study has not been replicated, and it is questionable whether there are any advantages
to picking up AM antibody-positive subjects amongst thyroid patients, since treatment
for PBC is largely symptomatic and no disease-modifying agents exist which can be used
in the asymptomatic phase.\textsuperscript{53} Given the high frequency of autoimmune thyroid disease
in PBC, however, it would seem worthwhile screening such patients with TPO
antibodies and TSH, as for patients with Addison’s disease.
TISSUE TRANSGlutaminase (TTG) antibodies

Diagnostic use

Endomysial antibodies, detected by immunofluorescence, are found in most patients with coeliac disease, having a sensitivity of 85–98% and specificity of 97–100%. TTG is the autoantigen recognized by these antibodies, and newer assays based on guinea pig or recombinant human TTG can be more sensitive but are less specific than endomysial antibodies. Tests for gliadin antibodies have moderate sensitivity but poor specificity. For example, in one recent series the sensitivity and specificity of endomysial antibodies in the diagnosis of coeliac disease was 90 and 98%, respectively; the corresponding values for TTG antibodies were 86 and 84%, and for gliadin antibodies 76 and 79%.

Coeliac disease is more common than previously thought, as milder forms of the disease have come to be recognized. Using both endomysial and TTG antibody screening of 3654 Finnish students, with small bowel biopsy of those who were positive, 1.5% had a positive antibody test and 66% of these had coeliac disease on biopsy, giving a prevalence of one in 99. It is unclear whether screening for such a common disease is worthwhile; although there are long-term risks from untreated coeliac disease, exclusion of dietary gluten is difficult in an asymptomatic individual.

Association with autoimmune thyroid disease

The prevalence of autoimmune thyroid disease is increased in coeliac disease. For instance, in one series 20.5% of coeliac patients had this complication, compared to 11.2% of controls. Dermatitis herpetiformis is accompanied by usually asymptomatic coeliac diseases; in 115 such patients, thyroid antibodies were found in 48%, compared to 16% of controls, and 10% had thyroid dysfunction.

Several studies have shown an increase in coeliac disease in thyroid autoimmunity (Table 3). Those with hypothyroidism who have undiagnosed coeliac disease, as shown by the presence of endomysial antibodies, have higher thyroxine requirements than patients who are antibody-negative. However, another study of 48 patients with Graves’ disease found only one with endomysial antibodies, in whom intestinal biopsy was normal and the antibodies disappeared after 3 years. How common such transient antibodies are in autoimmune thyroid disease is unclear.

In summary, the frequency of autoimmune thyroid disease in coeliac disease and dermatitis herpetiformis is high enough to consider screening such patients routinely.

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<thead>
<tr>
<th>Table 3. Frequency of coeliac disease or endomysial antibodies in autoimmune thyroid disease (AITD).</th>
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<td>AITD</td>
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<tr>
<td>Coeliac disease</td>
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<td>83</td>
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<tr>
<td>220</td>
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<tr>
<td>Endomysial antibodies</td>
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with TPO antibodies and TSH. The increased awareness of common, latent coeliac disease in the general population has made testing for this more common in patients with gastrointestinal or other unexplained symptoms. Although there have been recommendations for routine screening, I suggest the data so far indicate that TTG/endomysial antibody testing is best reserved for patients with thyroid disease who have any clinical features suggestive of coeliac disease, including osteoporosis and increasing or fluctuating thyroid hormone dosage requirements.

ACETYLCHOLINE RECEPTOR (ACHR) ANTIBODIES

Diagnostic use

Myasthenia gravis is uncommon, with a prevalence of around five per 100 000, although some estimates are higher. Diagnosis usually depends on the clinical history, electromyography and the response to edrophonium, supported by the presence of AChR antibodies, which are found in around 85% of patients. Only 50% of patients with ocular myasthenia have AChR antibodies. The antibodies are undoubtedly pathogenic, causing symptoms after transplacental transfer or injection into mice. Seronegative myasthenia gravis is due to the presence of antibodies against muscle-specific kinase or other autoantigens.

Association with autoimmune thyroid disease

The frequency of autoimmune thyroid disease is increased in myasthenia gravis. For instance, in 124 cases of myasthenia gravis studied in Belgrade from 1983 to 1992, thyroid autoimmune disease occurred in 7.3%, similar to previously published figures from Denmark. Myasthenia associated with autoimmune thyroid disease has a milder clinical expression, preferential ocular involvement and hence a lower frequency of AChR antibodies. In this Italian study, the prevalence of autoimmune thyroid disease was 28.5% in the myasthenic patients: 7.7% with Graves’ disease, 10.9% with euthyroid Hashimoto’s thyroiditis and 9.9% with autoimmune hypothyroidism. Much lower figures have been reported recently from Austria, challenging the dogma of a strong association, but the most recent survey, comprising 337 consecutive myasthenia patients from Athens, found that 39 (11.6%) had thyroid abnormalities, although unfortunately these were not detailed.

It would be very difficult to demonstrate an increased frequency of myasthenia gravis in autoimmune thyroid disease, given its rarity. However, AChR antibodies may be detected in a small proportion (8%) of patients with thyroid-associated ophthalmopathy, in the absence of myasthenia gravis. This suggests a sharing of autoantigenic targets in the two disorders. However, there is no justification for testing for AChR antibodies in patients with any form of autoimmune thyroid disease unless there are clinical reasons for suspecting myasthenia gravis.

SUMMARY

Autoimmune thyroid disease is frequently associated with organ-specific and non-organ-specific autoimmune disorders, and less common associations than those...
considered here are reviewed elsewhere.\textsuperscript{4} As a result there are increased frequencies of many non-thyroid autoantibodies in thyroid patients. It is important to recall that such autoantibodies are usually non-pathogenic and often mark a subclinical phase of disease. An overview of the data considered in this chapter is presented in Tables 4 and 5, along with tentative recommendations for screening. These recommendations take into account the frequency of each disease. No studies have yet been performed which show the cost–benefit of any of these recommendations. Some testing, such as in Addison’s patients, seems so obvious as to never be challenged, while others are more contentious. However, as treatments for each of these conditions improve, and high throughput, inexpensive autoantibody assays become established, the situation will undoubtedly change; now is the time to be assembling long-term, large studies of outcome to assess the practicalities and benefits of such screening.\textsuperscript{77}

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Prevalence (%)</th>
<th>Screening recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal cell</td>
<td>22–40</td>
<td>No\textsuperscript{a}</td>
</tr>
<tr>
<td>Intrinsic factor</td>
<td>3–7</td>
<td>Not unless other features suggestive of pernicious anaemia</td>
</tr>
<tr>
<td>Adrenal cortex/21-OH</td>
<td>1–2</td>
<td>No</td>
</tr>
<tr>
<td>Pituitary/α-enolase</td>
<td>8–28</td>
<td>No</td>
</tr>
<tr>
<td>Antinuclear</td>
<td>26</td>
<td>No</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>~5</td>
<td>No</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Tissue transglutaminase/endomysial</td>
<td>1–2</td>
<td>No\textsuperscript{b}</td>
</tr>
<tr>
<td>Acetylcholine receptor</td>
<td>&lt;1\textsuperscript{c}</td>
<td>No</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Worthwhile in patients with concurrent type 1 diabetes.
\textsuperscript{b} Perform in patients with osteoporosis or unusual thyroxine requirements.
\textsuperscript{c} Eight percent in patients with Graves’ ophthalmopathy.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence of TPO+TG antibodies (%)</th>
<th>Screening recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pernicious anaemia</td>
<td>Up to 50</td>
<td>Yes</td>
</tr>
<tr>
<td>Addison’s disease\textsuperscript{a}</td>
<td>11</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymphocytic hypophysitis</td>
<td>~10</td>
<td>Yes</td>
</tr>
<tr>
<td>Isolated ACTH deficiency</td>
<td>&gt;50</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>50</td>
<td>No\textsuperscript{b}</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>11–32</td>
<td>No</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>34</td>
<td>Yes</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>20–48</td>
<td>Yes</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>7–28</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Not associated with APS type 1 or 2.
\textsuperscript{b} More studies needed; may be worthwhile in older patients.
REFERENCES


