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2

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).[1] 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 1. Typical features of autoimmune polyglandular syndrome type 2.[3]

Prevalence	1 in 20 000
Inheritance	Autosomal dominant; variable penetrance; strong association with HLA-B8, DR3
Female:male ratio	3:1
Peak age of onset	30–40 years
Key endocrinopathies	Autoimmune thyroid disease (75%) Type 1 diabetes (55%) Addison's disease (45%)
Other major associations	Vitiligo (20%) Alopecia areata (6%) Pernicious anaemia (5%)