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Review

Autoimmune thyroid disorders

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ABSTRACT

Autoimmune thyroid diseases (AITD) result from a dysregulation of the immune system leading to an immune attack on the thyroid. AITD are T cell-mediated organ-specific autoimmune disorders. The prevalence of AITD is estimated to be 5%; however, the prevalence of antithyroid antibodies may be even higher. The AITD comprise two main clinical presentations: Graves' disease (GD) and Hashimoto's thyroiditis (HT), both characterized by lymphocytic infiltration of the thyroid parenchyma. The clinical hallmarks of GD and HT are thyrotoxicosis and hypothyroidism, respectively. The mechanisms that trigger the autoimmune attack to the thyroid are still under investigation. Epidemiological data suggest an interaction among genetic susceptibility and environmental triggers as the key factor leading to the breakdown of tolerance and the development of disease. Recent studies have shown the importance of cytokines and chemokines in the pathogenesis of AT and GD. In thyroid tissue, recruited T helper 1 (Th1) lymphocytes may be responsible for enhanced IFN-γ and TNF-α production, which in turn stimulates CXCL10 (the prototype of the IFN-γ-inducible Th1 chemokines) secretion from the thyroid cells, therefore creating an amplification feedback loop, initiating and perpetuating the autoimmune process. Associations exist between AITD and other organ specific (polyglandular autoimmune syndromes), or systemic autoimmune disorders (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, cryoglobulinemia, sarcoidosis, psoriatic arthritis). Moreover, several studies have shown an association of AITD and papillary thyroid cancer. These data suggest that AITD patients should be accurately monitored for thyroid dysfunctions, the appearance of thyroid nodules, and other autoimmune disorders.

Contents

1. Introduction

Autoimmune thyroid diseases (AITD) result from a dysregulation of the immune system leading to an immune attack on the thyroid. AITD are T cell-mediated organ-specific autoimmune disorders [1,2]. AITD are the most frequent autoimmune disorders, and the most common

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pathological conditions of the thyroid gland. The AITD comprise two main clinical presentations: Graves' disease (GD) and Hashimoto's thyroiditis (HT), that are both characterized by lymphocytic infiltration of the thyroid parenchyma. The clinical hallmarks of GD and HT are thyrotoxicosis and hypothyroidism, respectively.

The present study summarizes data about epidemiologic, risk factors and immunopathogenesis of HT.

1.1. Epidemiology

The prevalence of AITD is estimated to be 5% [3,4]; however, the prevalence of antithyroid antibodies (ATAs) without clinical disease may be even higher [5].

Studies [6–8] that have evaluated the changing epidemiology of HT have shown that: (1) women have a greater risk than men (about 4–10/1, female/male); (2) hypothyroidism from HT becomes more common with advancing age; (3) there are substantial geographic variability in the prevalence and incidence of HT; (4) prevalences of HT and thyroid antibodies differ with race; (5) ATA frequency increases with age, with a peak at around 45–55 years; and (6) populations that are iodine-sufficient have higher incidence of HT than those that are iodine-deficient.

In the Whickham study, the prevalence of spontaneous hypothyroidism from HT was 15/1000 in women, with mean age at diagnosis of 57 years, and less than 1/1000 in men [9]. The mean incidence of spontaneous hypothyroidism was 3.5/1000 in women and 0.6/1000 in men. Similar results have been recorded in other geographical areas [6].

The contemporary reported incidence rates of HT and hypothyroidism are higher than those in studies previously performed in similar regions [10].

However, it is not possible to know whether this is due to actual increased incidence or to the use of more accurate diagnostic procedures [11].

The HT is a prototypical organ-specific autoimmune disease. However, in many cases, AITD may be associated in the same patient with other organ-specific autoimmune attacks (such as in the case of type II autoimmune polyglandular syndrome), or less frequently with systemic autoimmune syndromes.

1.2. Risk factors

The mechanisms that trigger the autoimmune attack to the thyroid are still under investigation. Epidemiological data suggest an interaction among genetic susceptibility and environmental triggers as the key factor leading to the breakdown of tolerance and the development of disease.

1.3. Genetic susceptibility

Epidemiological evidence for a genetic susceptibility to AITD has been shown by the familial clustering of the disease (20–30% of AITD in siblings of affected patients), the sibling risk ratio (about 17) for AITD, and the increased prevalence of thyroid Abs (50%) of siblings of affected subjects [12]. The results of the twin studies show a concordance rate for AITD of 0.3–0.6 for monozygotic twins, compared to 0.00–0.1 for dizygotic twins [13,14]. From the twin studies, the heritability of GD has been calculated to be 79% in twin studies, and that of the presence of thyroid Abs was about 70% [14].

Several genes have been identified as significantly associated with the AITD and the presence of thyroid antibodies [15,16].

Among AITD genes detected by traditional case–control studies and tag single nucleotide polymorphism screening:

1. PTPN22 is involved in T-cell signal transduction through interaction with molecules essential for T-cell receptor signaling [17];
2. CTLA4 plays a role in inhibiting T-cell signaling [18];
3. Histocompatibility antigen (HLA) class II molecules play a key part in presenting exogenous antigens for recognition by CD4 + T-helper cells [19];
4 IL2RA encodes CD25 which is expressed on T-regulatory cells and is believed to be important in downregulating T-cell activity [20].

Other AITD genes were detected by case–control studies and confirmed by genome-wide association studies (GWAS):

1. FCRL3 is highly expressed during B-cell maturation and believed to both positively and negatively regulate B-cell signaling [21];
2. HLA class I molecules play a key role in presenting endogenous antigens, such a virally derived antigens, for recognition by CD8 + T cells [19];
3. TSHR is the receptor for TSH and is the primary autoantigenic target in GD [22].

Novel AITD genes have been detected by GWAS and Immunochip:

1. GDCG4p14 has been shown to be expressed in CD4 + T helper and CD8 + T cells [23];
2. BACH2 is expressed during B-cell maturation and is believed to control B-cell development and antibody production [24];
3. RNASET2 is expressed in CD4 + T-helper and CD8 + T cells [23];
4. FOXE1 is involved in thyroid gland morphogenesis and binds response elements in the thyroglobulin (Tg) and thyroid peroxidase promoters [25].

There are other AITD genes detected by GWAS and Immunochip whose function in AITD is currently unknown [15].

Interestingly among susceptibility genes whose function is known, 7/11 are involved in T cell function, strongly suggesting the importance of T cells in the immunopathogenesis of AITD.

1.4. Environmental factors

Environmental factors contribute to the occurrence of AITD for about 20%. Several environmental factors have been identified: radiation, iodine, smoking, infection, stress and drugs.

The link between environmental factors and autoimmunity is based on the principle that any injury resulting from infectious, chemical, radiological insults, may contribute to the activation of an innate immune response and, in susceptible individuals, to the development of AITD [26].

Radioiodine treatment of toxic goiter may be followed by the appearance of GD, even by Graves' ophthalmopathy (GO) [27]. Children exposed to radiation from Chernobyl showed a greater prevalence of thyroid autoantibody [28].

AITD tend to be more prevalent in areas with iodine sufficiency. Iodine supplementation of populations that were previously iodine deficient is associated with a transient increase of both autoimmune subclinical hypo- and hyperthyroidism [29].

Cigarette smoking has been associated with GD and with GO [30,31]. However, on the contrary, smoking decreases the risk of overt hypothyroidism as well as the prevalence of thyroid antibodies [32].

The thyroid is the organ with the highest selenium content because it expresses specific selenoproteins. After the discovery of myxoedematous cretinism following selenium repletion in iodine- and selenium-deficient children, many researches on links between thyroid and selenium have been published. Small amounts of selenium appear sufficient for adequate activity of deiodinases, however selenium status appears to have an impact on the development of thyroid pathologies. The importance of selenium supplementation in AITD has been emphasized [33].

Stress has been considered as a trigger factor for GD [34].