REVIEW ARTICLE

Autoimmune thyroid diseases and nonorgan-specific autoimmunity

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KEY WORDS

autoimmune thyroid disease, *CTLA4* gene, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome

ABSTRACT

Autoimmune thyroid diseases (ATD), as the most common organ-specific autoimmune disorder, is frequently accompanied by other organ- and nonorgan-specific autoimmune diseases. Although the exact pathogenic mechanism of the coexistence of autoimmune disorders has not been clearly defined, genetic and environmental factors, immune defects, and hormonal changes, may play a key role in polyautoimmunity. The role of human leukocyte antigen (HLA) haplotypes, HLA-B8 and -DR3, in the overlapping of autoimmune disorders was well supported by higher frequency of these haplotypes in primary Sjögren's syndrome (PSS) and ATD. In addition, polymorphisms of the cytotoxic T lymphocytic antigen 4 gene have been reported to be associated with many autoimmune disorders especially those coexisting with ATD. Definite noncasual association of ATD has been clearly documented in patients with PSS, rheumatoid arthritis, and systemic lupus erythematosus. Possible association with ATD is also considered in systemic sclerosis and dermatomyositis. Many authors documented a significantly higher prevalence of antinuclear antibodies (ANAs) in ATD patients in comparison with controls; however, the clinical significance of ANAs in this group is still unknown. The presence of other non-organ-specific antibodies has not been convincingly demonstrated. On the other hand, the prevalence of antithyroid antibodies as well as ATD is higher in patients with systemic connective tissue disease compared with the general population. Based on these data, there is no evidence for the utility of ANA testing in patients with ATD, but because of the high prevalence of ATD and antithyroid autoantibodies, it is clinically important to screen patients with autoimmune rheumatic disorders for the presence of thyroid autoimmunity.

Introduction Autoimmune thyroid disease (ATD) is the most prevalent organ-specific autoimmune disease characterized by the presence of antibodies against thyroid-specific components such as thyroglobulin, thyroid peroxidase, thyrotropin receptor antigen, and sodium iodine symporter. Currently, it is the most frequent cause of goiter in countries without iodine deficiency with the prevalence of 3% to 4% in the general population. The prevalence of antithyroid antibodies seems to be much higher than that of ATD and increases with age.[1]

It is well known that ATD is frequently accompanied by other organ- and nonorgan-specific autoimmune disorders, because there is the sharing of genetic and possibly environmental factors. These associations are well recognized in the autoimmune polyglandular syndrome, especially type 2, and also in about 4% of the patients with type 1. Recommendations have been issued to indicate the utility of screening for thyroid autoimmunity in patients with Addison's disease, lymphocytic hypophysitis, pernicious anemia, primary biliary cirrhosis, celiac disease, and myasthenia gravis.[2]

Association of ATD with nonorgan-specific autoimmune disorders, particularly rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and primary Sjögren's syndrome (PSS) has been demonstrated in several studies. Many authors documented a higher prevalence of nonorgan-specific autoantibodies, especially antinuclear antibodies (ANAs), in patients with ATD; however, their clinical significance is still uncertain.[3-5] On the other hand, the high prevalence of antithyroid antibodies and ATD in patients with autoimmune rheumatic disease has also been well documented by recent studies despite the fact that the pathogenic mechanisms of the coexistence of autoimmune disorders are still not completely recognized.

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Pathogenic mechanisms of autoimmunity in autoimmune thyroid disease and rheumatic disorders Although the exact pathogenic mechanisms of autoimmune disorders have not been sufficiently defined so far, most of the factors involved in the development of autoimmunity can be classified into 4 groups:

1 genetic factors: especially human leukocyte antigen (HLA) B8, HLA-DR3 and cytotoxic T lymphocytic antigen 4 (*CTLA4*) gene polymorphisms

2 immune defects: early activation of CD4 T lymphocytes specific for thyroid antigen, expression of major histocompatibility complex class II proteins induced by interferon γ, self-reactive CD4 T-cell stimulation of autoreactive B cells to secrete antithyroid antibodies, cytokine-regulated apoptotic pathways, and finally polymorphisms of *CTLA4* gene have been widely discussed in the current literature

3 hormonal factors: in particular estrogens, prolactin, melatonin, growth hormone, and gonadoliberine as immunostimulatory hormones whereas corticosteroids, progesterone, and testosterone are considered to be hormones with predominantly immunosuppressive effects

4 environmental factors: infectious agents, vaccines, smoking, drugs (interferon α, etc.), stress factors, endocrine disruptors and others.[6]

Role of the *CTLA4* gene The *CTLA4* gene is a member of the immunoglobulin superfamily and it is a costimulatory molecule expressed by activated T cells. At the same time, *CTLA4* is a structural homologue of CD28 but plays a negative regulatory role in T-cell response, i.e., suppression of immune response.

The human *CTLA4* gene is located on chromosome 2q33 and encodes the CTLA4 molecule, which is involved in the control of T-cell proliferation and accumulation of interleukin 2 and mediates T-cell apoptosis by binding the B7 molecules on antigen-presenting cells constituting the B7/CD28-CTLA4 costimulatory pathway of T-cell activation. Thus, the *CTLA4* gene is a strong candidate for susceptibility to T-cell-mediated autoimmune diseases. *CTLA4* gene polymorphisms have been shown to be associated with many autoimmune diseases. Three single nucleotide polymorphisms in the *CTLA4* gene, such as C318T, A49G, and CT60SNP, have been demonstrated to be associated with type 1 diabetes, RA, SLE, celiac disease, multiple sclerosis, and ATD. However, the results are inconsistent in various ethnic populations.[7,8]

To assess the relation of GG genotype or G allele of the A49G polymorphism in various ethnic cohorts with RA, a meta-analysis was performed by Shizong et al.[9] It included 10 studies (11 comparisons) with the *CTLA4* exon 1 A49G genotyping in 2315 patients with RA and 2536 controls. The subgroup and meta-regression analysis according to the ethnicity (European or Asian) demonstrated different scenarios concerning the role of *CTLA4* exon 1 A49G polymorphism in RA susceptibility for the 2 different subgroups. No effect of the G allele on susceptibility was observed in the European population. However, there was a significant association in Asians in both fixed and random-effect models. The results of the meta-analysis suggest that *CTLA4* exon 1 49G allele would not be a risk factor for RA in the European population but might play a role in RA susceptibility for Asians.[9]

Regarding the susceptibility to ATD, many studies confirmed the association between the promoter, exon 1 and 3' untranslated region *CTLA4* gene polymorphisms and ATD, including Grave's disease and Hashimoto's thyroiditis (HT). In addition, there have been studies investigating the relation between *CTLA4* gene and thyroid autoantibody (TAb) production. In a study by Zaletel et al.,[10] the authors provided evidence that CTLA4 A49G exon 1 polymorphism is associated with TAb status in patients with HT.[10]

There are only few reports comparing the frequency of the GG genotype of A49G polymorphism of the *CTLA4* gene in patients with both RA and HT with the frequency of this genotype in controls. In a study by Vaidya et al.,[11] there was an association between the CTLA4 G allele and RA, but the authors noted that this fact was largely explained by individuals with coexisting autoimmune endocrinopathies. In this study, the frequency of the G allele at CTLA4 A/G was significantly increased in probands with early RA compared with controls. Most of this increased frequency was attributable to RA individuals with coexisting HT.[11] In our study,[12] we demonstrated that the frequency of the GG genotype and G allele of A49G CTLA4 polymorphism in patients with both diseases was significantly higher than that in controls. In agreement with the previous studies in Caucasian cohorts, we did not confirm higher frequency of the GG genotype as well as G allele in patients with RA when compared with the control group. Moreover, the frequency of GG genotype in our group of patients with HT tended to be higher than in controls, although it did not reach statistical significance, possibly due to small sample size of HT patients.[12] Based on the above studies and our published data, we have suggested that the higher frequency of the G allele and GG genotype in patients with both diseases might be due to HT.[10-12]

Nonorgan-specific autoimmunity in patients with autoimmune thyroid disease Several studies showed that patients with ATD have significantly higher prevalence of ANAs, ranging from 25% to 55%.[3,5,13,14] Whether these findings are intrinsic to the disease or result from treatment or are coincidental has not yet been established. In addition, the clinical importance of this finding in patients with ATD is uncertain, and there are no data supporting the need for routine ANA testing in ATD patients. According to some authors, the appearance of nonorgan-specific antibodies

(especially ANAs) is probably largely a coincidental effect of polyclonal activation and antibody production by thyrocytes and immune cells.[2,3] In our study, the prevalence of ANA positivity was significantly higher in patients with ATD compared with the control group (45% vs. 14%). In agreement with the previous studies, there were no significant differences in the prevalence of other nonorgan-specific autoantibodies including extractable nuclear antigens, double-stranded DNA (dsDNA), Sjögren's syndrome A and B, rheumatoid factor, anticardiolipin (aCL) antibodies, and antineutrophil cytoplasmic antibodies.[13] The presence of these antibodies, including Sjogren's syndrome A and B, has been rarely reported. Some authors reported that anti-dsDNA antibody was detected in patients with Graves' disease, whereas others did not find these antibodies in patients with ATD.[15,16]

The presence of aCL reported in the previous studies is also controversial. While some authors confirmed a higher prevalence of aCL, others did not observe any in patients with ATD. Nevertheless, the presence of aCl in the cited studies has not been associated with clinical symptoms of antiphospholipid syndrome.[17,18]

Nonorgan-specific autoimmune diseases associated with autoimmune thyroid disease Although numerous papers have reported coexistence of ATD with other autoimmune disorders, there are only a few definite noncasual associations: PSS, RA, and SLE. A possible association is also considered in scleroderma and dermatomyositis.

Primary Sjögren's syndrome PSS is perhaps the most frequent rheumatic autoimmune disease associated with ATD, with a 10-fold higher prevalence compared with the general population. Recently, Hungarian authors documented a significantly higher prevalence of ATD in patients with PSS in comparison with the control group.[19]

A strong association between PSS and ATD obviously points to a common pathogenic mechanism, which is suggested, in particular, by the immunogenic predisposition and histology. The role of HLA-B8 and -DR3 in the overlapping conditions seems to be well supported by the high frequency of these haplotypes in both PSS and ATD. Regarding the histological findings, a number of authors described focal autoimmune sialadenitis in patients with ATD similarly to that observed in patients with PSS or primary biliary cirrhosis.[19,20]

Rheumatoid arthritis Recent studies have clearly demonstrated that there is an association between RA and ATD, which is in contrast to the former trials. The prevalence of antithyroid antibodies was reported to be from 12% to 37% and was significant in the majority of these studies.[4,21] In a recent study by Appenzeller et al.[22] performed on large groups of patients with ATD, the prevalence of other autoimmune disorders was up to 10% in Graves' disease and more than 14% in HT. RA was the most common coexisting autoimmune disease.

Systemic lupus erythematosus Despite the conflicting data regarding the relation between SLE and ATD, recent studies have documented a higher prevalence of primary hypothyroidism, subclinical hypothyroidism, and increased prevalence of antithyroid antibodies in patients with SLE. In a recent study, Sjögren's syndrome and positive rheumatoid factor were more frequently observed in SLE patients with ATD.[23,24]

Scleroderma (progressive systemic sclerosis) In the past, the association of scleroderma with ATD was not sufficiently confirmed; however, studies from the last 15 years reported a higher prevalence of antithyroglobulin (aTG) and antithyroid peroxidase (aTPO) in patients with systemic sclerosis in comparison with controls. In addition, patients with positive aTPO had a significantly higher frequency of HLA DR15 haplotype than those who were aTPO-negative. Therefore, HLA DR15 may represent the immunogenic marker of aTPO production in patients with scleroderma. In a recent study, 38% of patients with systemic sclerosis were positively screened for the coexistence of ATD, and ATD was also the most prevalent coexisting autoimmune disease.[4,25]

Dermatomyositis/polymyositis Although the association of dermatomyositis/polymyositis with ATD has not been definitely confirmed so far, a number of authors observed a 25% prevalence of primary hypothyroidism in patients with dermatomyositis/polymyositis.[26]

Autoimmune thyroid disease and antithyroid antibodies in patients with rheumatic disorders Higher prevalence of ATD and antibodies against thyroid specific components (mostly aTG and aTPO) has been confirmed by many studies; the reported prevalence ranged from 10% to 32%.[4,27] The prevalence of ATD in our cohort of patients with RA and SLE was 24% and was slightly higher in RA patients compared with those with SLE.[12] In a study by Bianchi et al.[28] thyroid enlargement was 2- to 3-fold higher in patients with rheumatic disorders compared with controls. Moreover, patients showed a 2- to 4-fold increase in the prevalence of thyroid antibodies compared with controls. Numerous other studies documented the prevalence of thyroid antibodies in patients with SLE or RA, ranging from 9% to 19% with or without statistical significance. Hypothyroidism was more frequent than hyperthyroidism. In a study by Biró et al.,[29] 8.2% of systemic autoimmune patients had either HT or Graves' disease. The results of the above studies indicate that due to a higher frequency of thyroid autoimmunity in patients with rheumatic diseases, especially RA, SLE, and PSS, it is clinically important to screen these patients for the coexistence of ATD.[30]

Conclusion Although the association of ATD with nonorgan-specific autoimmunity has been confirmed by numerous studies, there is no evidence for the utility of ANA testing in patients with ATD. On the other hand, because of the high prevalence of ATD and antithyroid autoantibodies, it is clinically important to screen patients with autoimmune rheumatic disorders for the presence of thyroid autoimmunity.

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Autoimmunologiczne choroby tarczycy i nieswoiste narządowe zjawiska autoimmunologiczne

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SŁOWA KLUCZOWE

autoimmnologiczne choroby tarczycy, gen *CTLA4*, reumatoidalne zapalenie stawów, toczeń rumieniowaty układowy, zespół Sjögrena

STRESZCZENIE

Najczęstszym narządowoswoistym chorobom autoimmunologicznym towarzyszą często inne narządowoswoiste lub narządowonieswoiste choroby autoimmunologiczne. W zjawisku współistnienia chorób immunologicznych dopatruje się roli czynników genetycznych i środowiskowych, zaburzeń odporności i zmian hormonalnych, ale dokładny mechanizm współwystępowania chorób autoimmunologicznych nie został jeszcze poznany. Na udział występowania antygenów HLA-B8 i -DR3 w zespołach nakładania się zaburzeń autoimmunologicznych wskazuje duża częstość występowania tych haplotypów u chorych na pierwotny zespół Sjögrena i autoimmunologiczne choroby tarczycy (*autoimmune thyroid diseases* – ATD). Dodatkowo u chorych na ATD współistniejące z innymi zaburzeniami autoimmunologicznymi wykazano występowanie polimorfizmu genu kodującego antygen 4 cytotoksycznych limfocytów T (*CTLA4*). Nieprzypadkowe współistnienie ATD wykazano u chorych na pierwotny zespół Sjögrena, reumatoidalne zapalenie stawów i toczeń rumieniowaty układowy. Współwystępowanie ATD sugeruje się także w twardzinie układowej i zapaleniu skórno-mięśniowym. Wielu autorów wskazuje na istotnie częstsze występowanie przeciwciał przeciwjądrowych (*antinuclear antibodies* – ANA) u chorych na ATD w porównaniu z grupą kontrolną, chociaż znaczenie kliniczne ANA u tych chorych nie jest znane. Występowanie innych nieswoistych narządowo autoprzeciwciał nie zostało jednoznacznie udowodnione. Z drugiej strony występowanie przeciwciał przeciwtarczycowych oraz ATD jest częstsze u chorych na układowe choroby tkanki łącznej niż w populacji ogólnej. Na podstawie tych danych, nie udowodniono przydatności oznaczenia ANA u chorych na ATD, jednak ze względu na dużą częstość występowania ATD i przeciwciał przeciwtarczycowych wskazane jest wykonanie badań przesiewowych w kierunku autoimmunologicznych chorób tarczycy u chorych na autoimmunologiczne choroby reumatyczne.

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