

Chronic urticaria and autoimmune thyroid disease: is there a link?

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Abstract

Chronic idiopathic urticaria (CIU) is a common and frustrating disorder. A subset of patients with CIU has been classified as autoimmune on the basis of two main findings: association with thyroid autoimmunity and anti-IgE and/or anti-IgE receptor antibodies. There is growing evidence that some cases of CIU are associated with thyroid autoimmunity. Patients with CIU have an increased frequency of Hashimoto thyroiditis with the presence of antibodies to thyroglobulin or a microsomal-derived antigen (peroxidase), even in euthyroid patients. No broad non-specific autoimmunity is present. Antibodies reactive with $Fc_\epsilon RI$, the high-affinity IgE receptor are found in sera of 10–40% of patients with CIU. A smaller subset of patients with CIU lack anti- $Fc_\epsilon RI$ antibodies and have anti-IgE antibodies that cross-link $Fc_\epsilon RIs$ occupied by IgE. There are a minority of CIU patients that lack such antibodies, but can degranulate basophils by a serum factor that has not yet been determined. Most patients with anti-IgE antibodies have an IgG antibody directed against the 34 kD α subunit of the IgE receptor. There are no data to suggest that any of the anti thyroid antibodies is pathogenic in terms of CIU, and most likely these are associated, parallel, autoimmune events. Screening for thyroid autoimmunity and function is advisable in all patients with CIU for the early identification of patients requiring either treatment of underlying thyroid dysfunction or follow-up.

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1. Introduction

One of the interesting clinical associations is that of chronic idiopathic urticaria (CIU) and thyroid disease. CIU occurs in persons who do not have an increased incidence of atopic dermatitis, allergic rhinitis, or asthma compared with the incidence of these disorders in persons without CIU. Their IgE level, as a group, is within normal limits. CIU does not appear to be an allergic

reaction in the classic sense, because IgE antibody is not involved and no external allergen is needed to initiate or perpetuate the process. Most CIU are characterized by a non-necrotizing perivascular mononuclear cell infiltrate with an accumulation of mast cells. Patients with vasculitis and chronic urticaria are a separate subpopulation in whom the cause and pathogenesis of hive formation probably involves immune complexes, complement activation, anaphylatoxin formation, histamine release, and neutrophil accumulation, activation, and degranulation. A subset of patients CIU has been

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recently classified as autoimmune on the basis of two main findings: association with thyroid autoimmunity and with anti-IgE and/or anti-IgE receptor antibodies.

2. Clinical association of CIU and thyroid disease

There is growing body of evidence that some cases of CIU are associated with thyroid autoimmunity. The first studies of autoimmunity in patients with CIU reported that patients with CIU have an increased frequency of Hashimoto thyroiditis [1,2]. The association was with the presence of antibodies to thyroglobulin or a microsomal-derived antigen (peroxidase), even in euthyroid patients. The incidence of abnormal thyroid function, either increased or decreased thyroxine (T_4) or increased or decreased thyroid-stimulating hormone (TSH) or both, was 12–19% [3,4]. A detailed study of auto antibodies present in patients with urticaria none of whom had thyroid showed that antibodies to thyroid peroxidase (TPO) and rheumatoid factor were found significantly more common in urticaria (20 and 16%, respectively) than in controls (0%), but broad non-specific autoimmunity was not found [5]. To examine if anti thyroid antibodies are unique to CIU or appear in any chronic urticaria, a further study was performed to examine the prevalence of thyroid antibodies in two distinct series of chronic urticaria: of known cause (group A) and idiopathic (group B) [6]. Twenty-three patients of group A (33%) and 12 (M/F:4/8) of group B (23%) tested positive for at least one type of thyroid antibody. The difference was not statistically significant. Thyroid disease or altered serum TSH levels (requiring treatment) were present in 39% of group A and 42% of group B seropositive patients. These results were not expected on the assumption that autoimmune phenomena are a specific pattern of CIU. The study, thus, revealed that chronic urticaria, either of known cause or idiopathic (CIU), is significantly associated with thyroid autoimmunity.

3. Pathogenesis of CIU

While the pathogenesis of CIU is not completely understood, mast cell activation is thought to be

of major importance. Antibodies reactive with $Fc_\epsilon RI$, the high-affinity IgE receptor, were found in sera of 10–40% of patients with CIU [2,7]. These antibodies have the potential to cross-link $Fc_\epsilon RI$ s on mast cells and basophils. This leads to the release of mediators, chemokines, and cytokines. A smaller subset of patients with CIU lack anti- $Fc_\epsilon RI$ antibodies and have anti-IgE antibodies that cross-link $Fc_\epsilon RI$ s occupied by IgE. Such antibodies were not specific for CIU, however, and were detected in patients with atopic dermatitis. A large number of patients with CIU have a positive autologous skin test [8]. Most members of subpopulation of positive patients studied in much greater detail were found to have an IgG antibody directed to the α subunit of the IgE receptor [9]. By using rat basophil leukemia cells transfected with the human α subunit, the release of histamine or the enzyme α -hexosaminidase could be demonstrated. Thus, it appeared that the antibody could cross-link the IgE receptor (α subunit) and degranulate the cells. The incidence of such antibodies is approximately 35%, and an additional 5–10% of patients have anti-IgE antibodies rather than anti-IgE receptor antibody. Patients with CIU and Hashimoto's thyroiditis but not patients without Hashimoto's thyroiditis had anti- $Fc_\epsilon RI$ antibodies in their sera that could induce degranulation of normal basophils [4]. Some sera from patients with chronic urticaria and Hashimoto's thyroiditis caused degranulation of normal basophils in the absence of anti- $Fc_\epsilon RI$ antibodies. The factor causing basophil degranulation was not determined [4]. These results showed that Hashimoto's thyroiditis likely represents a marker of autoimmunity, rather than being a direct cause for CIU. Immunoblot analysis demonstrated that anti-IgE receptor antibodies bind to the 34-kd cloned α subunit [10]. The pathogenesis of autoimmune diseases typically involves interference with the function or destruction of tissues by auto antibodies or auto reactive T cells. Some cases of CIU are exceptions in that anti-thyroid-stimulating hormone receptor (TSHR) antibodies react as agonists. Recently a case of CIU was described in association with Graves' disease, where anti $Fc_\epsilon RI$ antibodies were detected in addition to TSHR antibodies [11]. This report showed the coexistence of these two conditions

were mediated by a different anti receptor antibody. The mechanism by which thyroid autoimmunity is associated with CIU is poorly understood. A cross-linking of IgE receptors of mast cells induced by anti thyroid antibodies may presumably be a cause of histamine release. The presence of anti-TPO IgE in a patient with chronic urticaria and suggested that these IgE autoantibodies might play a pathogenetic role in urticarial symptoms, sensitizing mast cells and inducing degranulation after exposure to the specific circulating antigen (released as a result of autoimmune thyroid damage) [12]. It has been also hypothesized that anti-TPO IgE could cross-react with peroxidase contained in vegetables and that the ingestion of some peroxidase-containing vegetables could trigger urticaria. A more recent report, however, of 38 patients with chronic urticaria showed these patients had only anti-TPO IgG, but no patient was positive for anti-TPO IgE [13]. The results indicate that the detection of IgE specific for TPO is an occasional finding and that these antibodies are unlikely to play a pathogenic role in most cases of CIU [13]. There are no data to suggest that any of the anti thyroid antibodies is pathogenic in terms of CIU, and most likely these are associated, parallel, autoimmune events.

4. Treatment

Current main treatment of chronic urticaria is by antihistamines. While the association of chronic urticaria and thyroid autoimmunity is not well understood, the potential use of thyroxine in the treatment of chronic urticaria in patients with thyroid autoimmunity is even less well established. There are conflicting reports on the results of such therapy [4]. Treatment with thyroxine was reported to alleviate the symptoms of urticaria in some cases with concomitant decrease in anti thyroglobulin antibodies. Some reports advocate that patients with chronic urticaria should be screened for evidence of thyroid autoimmunity, and that a trial of thyroxine therapy for those who have thyroid autoimmunity can be rewarding for the clinical improvement by the suppression of chronic thyroid stimulation [14]. Supplementation beyond that required for achieving the euthyroid state is cur-

rently not recommended. Thyroid function tests are not enough to rule out thyroid disease, and thyroid antibody tests should be carried out in all patients with CIU. The assumption that CIU and thyroid disease are parallel, autoimmune events can explain the lack of effectiveness of anti thyroid treatment in some patients with CIU and anti TPO antibodies.

5. Conclusion

CIU and thyroid autoimmune disease are associated conditions in some patients with the presence of anti-IgE and/or anti-IgE receptor antibodies and anti thyroid antibodies. At present it seems that these two conditions are parallel autoimmune diseases and that anti thyroid antibodies do not play a direct role in the pathogenesis of CIU. Screening for thyroid autoimmunity and function is advisable in all patients with CIU for the early identification of patients requiring either treatment of underlying thyroid dysfunction or follow-up.

Take-home messages

- A subset of patients with CIU has been classified as autoimmune based on association with thyroid autoimmunity and anti-IgE and/or anti-IgE receptor antibodies.
- There are no data to suggest that anti thyroid antibodies have a pathogenic role in CIU.
- CIU and thyroid disease are most likely associated, parallel, autoimmune events.
- Screening for thyroid autoimmunity and function is advisable in all patients with CIU for the early identification of patients requiring either treatment of underlying thyroid dysfunction.

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The World of Autoimmunity; Literature Synopsis

Risk factors for development of systemic lupus erythematosus. Allergies, infections, and family history

In a report by Cooper et al. (*J Clin Epidemiol* 2002;55:982–9), they examined various risk factors associated with systemic lupus erythematosus (SLE). The etiology of SLE has long been sought. Based on murine models of SLE, familiar association and linkage studies, and twin concordance, a genetic basis seems evident, however it is still unclear what role the environment plays and few epidemiologic studies have addressed this issue.

This study, the Carolina Lupus Study, identified 265 newly diagnosed SLE patients and carried out a 60 minute in person interview. The results of the study were as following:

- a. SLE patients were more likely than the control to report of allergies to medications especially to sulpham drugs and antibiotics, and SLE occurred more often in those with a high school education or less (odds ratio (OR) 3.8) compared to those with more than a high school education (OR 2.9). Hives were associated with increased SLE (OR 1.8). There was a weak association (not significant) with food allergies, psoriasis, and asthma
- b. SLE patients were more likely to have had a history of herpes zoster (OR 2.5), and have had frequent (> 1/yr) cold sores (OR 2.8) and flu. There was little association with EBV virus, implanted medical devices, or hepatitis B vaccine. There was an increased risk of SLE in those who had had a history of blood transfusions among African Americans (OR 3.8)
- c. Finally, a family history of SLE (parents, siblings) was associated with an increased risk of SLE (OR 3.3), as well as other systemic autoimmune diseases

This study showed possible associations between environmental factors and the risk of developing SLE. For the future, such studies may provide insight into the pathogenesis of an age-old illness.