

Allergy and Systemic Diseases: The Case of Chronic Urticaria and Thyroid Disease

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Allergy by virtue of its pathophysiology is by itself a systemic condition manifesting itself in various organs. Allergy commonly presents itself in the skin, upper and lower airways and gastrointestinal tract. The common mechanism of the different manifestations is cross-linking of the immunoglobulin E receptors by an antigen, leading to the release of pre-formed granules from mast cells and induction of newly formed mediators, which in turn lead to the allergic inflammation. Allergy can, however, be associated with other diseases unrelated to the allergic process. One of the fascinating associations is that of chronic idiopathic urticaria and thyroid disease.

CIU occurs in persons who do not have an increased incidence of atopic dermatitis, allergic rhinitis, or asthma, as 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, since IgE antibody is not involved and no external allergen is needed to initiate or perpetuate the process. Most CIU cases are characterized by a non-necrotizing perivascular mononuclear cell infiltrate with an accumulation of mast cells. Patients with vasculitis and chronic urticaria constitute a separate subpopulation in whom the cause and pathogenesis of hive formation probably involve immune complexes, complement activation, anaphylatoxin formation, histamine release, and neutrophil accumulation, activation and degranulation.

A subset of CIU patients has recently been classified as autoimmune on the basis of two main findings: association with thyroid autoimmunity and with anti-IgE and/or anti-IgE receptor antibodies. There is growing 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, or increased or decreased thyroid-stimulating hormone, or both, was 12–19% [3,4]. A detailed study of autoantibodies present in patients with urticaria – none of whom had thyroid disease – showed that antibodies to thyroid peroxidase were found significantly more common in urticaria (20%) than in controls (0%), but broad non-specific autoimmunity was not found [5]. 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 in group A (33%) and 12 (M/F:4/8) in 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.

While the pathogenesis of CIU is not completely understood, mast cell activation is thought to be of major importance. Antibodies reactive with FcεRI, the high affinity IgE receptor, were found in the sera of 10–40% of patients with CIU [2,7]. These antibodies have the potential to cross-link FcεRIs on mast cells and basophils. This leads to the release of mediators, chemokines and cytokines. A smaller subset of patients with CIU lack anti-FcεRI antibodies and have anti-IgE antibodies that cross-link FcεRIs containing IgE. Such antibodies were not specific for CIU, however, and were detected in patients with atopic dermatitis. Many patients with CIU have a positive autologous skin test [8]. In a subpopulation of positive patients studied in much greater detail, most 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 about 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-FcεRI antibodies in their sera that could induce degranulation of normal basophils [4]. Some sera from patients with chronic urticaria and Hashimoto's thyroiditis exhibited degranulation of normal basophils in the absence of anti-FcεRI 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 autoantibodies or autoreactive T cells. Some cases of CIU are exceptions in that

CIU = chronic idiopathic urticaria

TSH = thyroid-stimulating hormone

anti-thyroid-stimulating hormone receptor antibodies react as agonists. Recently, a case of CIU was described in association with Graves' disease, where anti-Fc ϵ RI antibodies were detected in addition to TSHR antibodies [11]. This report showed that 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-thyroid peroxidase IgE in a patient with chronic urticaria 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 also been 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. However, a more recent report showed that 23 patients with chronic urticaria had only anti-TPO IgG, but none 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.

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 a 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 contribute to clinical improvement by the suppression of chronic thyroid stimulation [14]. Assay of thyroid hormone and anti-thyroid antibodies should be performed in patients with chronic urticaria. The discovery of Hashimoto's thyroiditis with chronic urticaria requires thyroid hormone replacement not only in hypothyroid but also euthyroid patients. Supplementation beyond that required to achieve the euthyroid state is currently not recommended. Thyroid function tests are not sufficient 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.

In conclusion, CIU and thyroid autoimmune disease are associated 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.

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