

Chronic urticaria and thyroid disease

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For many investigators, the search for potential causes of chronic urticaria (CU) is likened to that for the Holy Grail. Acute urticaria is a common condition, estimated to occur in 20% of the world's population [1], and its cause can be identified relatively frequently. In chronic urticaria, however, the specific cause determined in no more than 30% of cases (a generous estimate) [2]. Interest in the association of autoantibodies with urticaria and angioedema has been studied for years, and reports of symptoms occurring in the setting of hyperparathyroidism [3,4], hypoparathyroidism [5], systemic lupus erythematosus [6,7], gastrointestinal disease [8,9], and hematologic malignancies [10,11] are common in the medical literature. The importance of autoantibodies to the high affinity receptor for IgE and to IgE itself has become appreciated (see the article by Grattan elsewhere in this issue). This article focuses on the connection between CU, angioedema, and autoimmune thyroid disease.

Historical review

The association of thyroid disease with pruritus and urticaria dates back to review articles from the 1950s and 1960s [12,13], and in 1971, a report by Isaacs and Ertel suggested that the urticaria of hyperthyroidism might be related to an autoimmune phenomenon [14]. Since then, many other investigators have commented on a possible connection between autoimmune thyroid disease and

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chronic urticaria. These early studies reported that patients with Grave's disease and elevated levels of what was then called long-acting thyroid stimulator immunoglobulin tended to have more dermatologic manifestations than patients with Hashimoto's disease. Unlike the situation with acute urticaria, antihistamines had little to no effect on the resolution of urticarial lesions, and the hives did not clear completely until the underlying thyroid state was controlled [14]. In two large observational studies from the 1980s, thyroid autoimmunity was observed to occur in patients with chronic urticaria with greater frequency than other potential causes. Small and Lerman [15] described their findings in 154 patients with CU, six of whom were hyperthyroid, and Leznoff et al reported 17 (12.1%) of 140 consecutively evaluated patients with CU and elevated levels of thyroid microsomal antibodies [16]. As was the case with the initial reports, resolution of symptoms in patients did not occur until the underlying thyroid state was corrected. In the report by Leznoff, 14 of the 17 patients described were initially euthyroid. Of those, five of seven patients treated with levothyroxine had resolution or improvement in their urticaria. Therapy was justified on the basis of presumed autoimmune thyroiditis. Later reports by Ertel [17] and MacKechnie [18] emphasized the potential benefits of screening patients with CU for thyroid dysfunction, as pruritus or urticaria may be the initial presenting symptom in patients with thyrotoxicosis. Resolution of CU associated with thyrotoxicosis has been seen in patients treated with antithyroid medication [19] and those treated with radioactive iodine [20].

Three of the patients who were euthyroid in the Leznoff study developed hypothyroidism. The association of hypothyroidism with CU was reported subsequently by Lanigan et al in a letter to the editor of *Lancet* in 1984 [21]. In their report, 5 of 25 patients with CU had coexisting hypothyroidism, three of whom had positive antimicrosomal antibodies. An additional five patients without myxedema had elevated levels of antimicrosomal antibodies. One patient with hypothyroidism and two patients without hypothyroidism also had positive antithyroglobulin antibodies.

The prevalence of antithyroid antibodies in the normal population has been estimated at 3% to 6% [22], and they commonly are found in association with other autoimmune conditions, such as pernicious anemia [23] and vitiligo [24]. From a pool of 624 patients with presumed idiopathic CU and angioedema, Leznoff and Sussman summarized the clinical and laboratory features of 90 patients with evidence of thyroid autoimmunity (prevalence, 14%) [24]. Realizing that this association was statistically significant, 46 patients were treated with l-thyroxine therapy, eight of whom had remission within 4 weeks of therapy. Four patients with high thyroid antibody titers had repeated exacerbations when therapy was discontinued and had repeated remissions when therapy with l-thyroxine was resumed. Supposing that the l-thyroxine was suppressing the underlying thyroid autoimmunity or serving as replacement therapy in patients with hypothyroidism or those destined to have hypothyroidism, many investigators have speculated on the potential cause-and-effect role that thyroid autoantibodies have in CU.

In 1995, unlike other reports that implicated thyroid disease states as the underlying factor causing urticaria, patients who were euthyroid and had antithyroid antibodies and CU were shown to have resolution of their hives with thyroid hormone replacement therapy [25]. This observation led many to speculate on the specific role of thyroid autoantibodies as an etiologic factor and the treatments that might be employed to combat such a condition.

Clinical presentation

In adults and children, the most common clinical symptoms of thyroid-induced urticaria are dermatologic. As in cases of classic chronic idiopathic urticaria, individuals complain of typical raised, erythematous, occasionally coalescing, warm, pruritic wheals. Symptoms of angioedema, whether peripheral or central, have been estimated to occur in roughly 4 to 9% of cases [16,26]. Occasionally, patients present with symptoms of anaphylaxis and cholinergic-like or dermatographic (delayed pressure) urticaria, with lesions that are concentrated in areas of warmth, moisture, or pressure. Most individuals experience symptoms on a daily basis, and many are refractory to standard treatment such as H₁ and H₂ antihistamines (systemic, oral, or topical). Some patients also have incomplete or minimal responses to parenteral, oral, or topical corticosteroids. Response to off-label use of anti-inflammatory agents, such as calcium-channel blockers, methotrexate, cyclosporin, and dapsone, has not been reported in this specific condition. Similarly, newer agents, such as leukotriene antagonists, and nonsteroidal T-cell-inhibiting agents, such as pimecromilus or tacrolimus, have yielded mixed results and have not been studied extensively in this patient population. Historical or physical examination data that suggest an underlying thyroid or other autoimmune condition should raise the possibility that these conditions are contributing to or are causative of the urticaria.

Evaluation

Many authors have advocated assessment for the presence of thyroid antibodies and thyroid function as part of the routine evaluation for patients with refractory urticaria [26–31]. As autoimmune conditions can overlap or be seen concomitantly, evaluation for additional autoimmune conditions other than thyroid disease also has been proposed [31]. Over the years, a number of other direct or indirect measures of immune activation, complement activation, histamine release, or neuroendocrine function (eg, epinephrine, norepinephrine, acetylcholine, substance P, vasoactive intestinal peptide) have been suggested [32,33]. Some investigators have seen symptoms reproduced on autologous skin testing [30,31,34]. As interest has grown in the potential involvement of the IgE receptor [35,36], tests have become available to evaluate the presence of IgG antibodies to the IgE receptor and the presence of antithyroid IgE antibodies [37,38]. Kikuchi

et al have reported that antithyroid antibodies are found more frequently in patients with antibodies against the high affinity receptor for IgE [39]. Skin biopsies of involved and uninvolved skin have been performed in many patients with CU, but the authors are not aware of reports that specifically examine urticarial lesions in patients with antithyroid antibodies. CU is characterized by the presence of inflammatory cells, such as activated T cells, eosinophils, and basophils, in skin biopsies [40]. Mast cells do not seem to have a major role in CU [41]. Some investigators have found increased histamine release and increased levels of interleukin 3 (IL-3), tumor necrosis factor α , granulocyte-macrophage colony-stimulating factor, MCAF, MCP-1, and RANTES in lesional and perilesional skin [40–42]. Other investigators have shown that the cytokine pattern seen in biopsy specimens of active lesions from patients with CU resembles a T helper cell type 0 (T_H0) cytokine profile with increased levels of IL-4, IL-5, and interferon γ mRNA⁺ cells [43]. Few differences have been found in the numbers of activated neutrophils and eosinophils in skin biopsies from patients with CU compared with the numbers in biopsies of patient with and without anti-IgE and anti-Fc ϵ RI antibodies [44]; it is likely that urticarial lesions from patients with antithyroid antibodies have similar histology. With a large number of cytokines and activated inflammatory cells present in lesional and perilesional skin, it has been suggested that the threshold for the development of acute or chronic lesions may be lowered [41]. Factors that trigger that inflammatory response remain to be identified.

Potential mechanisms of disease presentation and resolution

It has been argued that the presence of thyroid autoantibodies and CU is a reflection of a more generalized autoimmune state [39]. From this point of view, the antithyroid antibodies are epiphenomena relative to the CU; however, the authors' experience that treatment of patients with thyroid hormone effectively resolves the urticaria leads them to postulate that thyroid glandular inflammation is a central feature of this association. Admittedly, the mechanisms whereby autoimmune thyroid disease may induce urticaria remain unclear and unstudied. The authors propose that when the thyroid gland is inflamed because of spontaneously occurring (or virally induced) autoantibodies, normally sequestered thyroid antigens are released into the local and systemic circulation, stimulating a further immune response. This immune response is characterized by the presence of antibodies to thyroid components—antithyroglobulin or antimicrosomal (specifically antiperoxidase) antibodies. As mentioned earlier, it is debatable as to whether the antibodies themselves are involved in the pathogenesis of the urticarial lesions or are an epiphenomenon. A part of the argument against the importance of the antibodies is the observation that disease remission does not parallel changes in antibody levels; however, it is possible that their presence may serve as a marker of immune activation involving other thyroid-dependent mechanisms not yet determined, rather than actively causing the urticaria.

As mentioned earlier, successful treatment of thyroid-induced urticaria seems to be related to suppression of thyroid glandular inflammation. This suppression has been accomplished with surgery [45], antithyroid medication [17,19,20], and thyroid hormone supplementation [23]. Though the indications for surgery in the setting of a malignancy, tapazole in the presence of Grave's disease, or thyroid hormone replacement in Hashimoto's thyroiditis may seem obvious, treatment of patients who are euthyroid and have antithyroid antibodies with suppressive hormone replacement is not obvious, although it has been used with apparent success [25]. These patients have subclinical autoimmune thyroiditis, and they are being treated before they have shown any evidence of hyperthyroidism or hypothyroidism. One of the authors (A.L. Schocket) successfully treated two patients with daily unremitting urticaria and a strong family history of thyroid disease (specifically hypothyroidism) with thyroid suppression who did not have detectable antithyroid antibodies. Because these two individuals responded in a similar fashion to patients with antithyroid antibodies, it is possible that non-humoral immune factors have a role in this disease.

No double-blind, placebo-controlled studies support or disprove the hypothesis that thyroid suppressive therapy can alter the course of urticaria in patients who are euthyroid and have antithyroid antibodies. There is no general agreement as to the possible mechanisms whereby thyroid autoimmunity could contribute to CU or whereby suppression of thyroid gland activity may lead to resolution of CU in this setting.

The authors propose that the following scenario could unify these concepts:

- The mechanisms leading to the presence of thyroid autoimmunity are unclear and reviewed elsewhere. Thyroid stimulation by thyroid-stimulating hormone (TSH) drives glandular activity and potentially exacerbates inflammation, even in susceptible patients who are euthyroid. Some patients are already hypothyroid, suggesting that portions of the gland have been destroyed. Susceptible patients could have polymorphisms in the TSH receptor and enhancement of normal receptor signaling.
- Inflammation, caused by the presence of autoantibodies, disrupts the normal architecture of the gland and leads to cellular disarray and the release of sequestered antigen.
- These sequestered antigens are perceived as nonself and induce a low-grade autoimmune response.
- Products or mediators of this autoimmune response affect cutaneous mast cell activation or mediator release thresholds. Products such as thyroid protein immune complexes could be formed that activate the classical complement pathway, leading to the generation of complement split products C3a and C5a. As skin mast cells have receptors for these products, degranulation can occur. Alternatively, various histamine-releasing factors could be generated as a result of the autoimmune response, leading to altered mast cell release thresholds, degranulation, and release of mast cell mediators.

- Once thresholds of mast cell mediator release are reduced, these cells become susceptible to further stimulation by physiologic levels of endogenous compounds, such as substance P. This mechanism may be similar to that seen in exercise-induced anaphylaxis, in which secondary factors are necessary for disease initiation.
- Thyroid gland suppression ultimately is accomplished with thyroid hormone. It is postulated that this suppression occurs by the direct suppressive effect of l-thyroxine on TSH production by the anterior pituitary gland. Alternatively or additionally, l-thyroxine may exert its effect on glandular inflammation by directly influencing the function of altered thyroid peroxidase (ie, altered because of autoantibodies against the enzyme). In either event, TSH production is diminished.
- As TSH is reduced to negligible levels (not just normal levels; discussed later in article), thyroid gland inflammation begins to recede, leading to reduced cellular release of sequestered antigen.
- Decreased release of sequestered antigen ultimately leads to a reduction in immune (ie, autoimmune) response and a reduction in immunologic reactants. This change ultimately leads to a return of normal thresholds of mast cell release and normalization of the clinical state.

Although this scheme is highly speculative, it attempts to explain potential mechanisms of disease and treatment response, particularly with regard to the effect of thyroid hormone. There are many unknowns, including the specific thyroid antigens that may be important. Though the models propose the release of sequestered thyroid antigens, no investigators successfully have identified such a material. It has been suggested that thyroid peroxidase (TPO) may be key (Charles Kirkpatrick, MD, personal communication, 2003), because TPO serves a functional role (as an enzyme) and an antigen role (as the substrate for anti-TPO antibodies). Altering its level or function could have a direct effect on the generation of altered thyroid peptides that ultimately may be the stimulating thyroid antigens. Similar theories have been suggested regarding the role that antibodies to tissue transglutaminase have in contributing to the pathology of celiac disease [46,47]. Alternatively, it has been suggested that TSH suppression plays a critical role in hive resolution. In this situation, the explanation for the effect of l-thyroxine is to suppress the production of TSH by the anterior pituitary gland and decrease glandular activity.

Treatment

It would be inappropriate to consider all patients with CU as potential candidates for l-thyroxine therapy. Assuming that other causes for CU have been eliminated, candidates for l-thyroxine treatment would have antithyroid antibodies and no other underlying medical condition in which l-thyroxine therapy would be contraindicated (eg, underlying thyroid malignancy, severe osteoporosis).

sis, uncontrolled atrial fibrillation). Therapy typically is initiated at 0.1 mg/d, though lower starting doses can be used in high-risk patients. In patients treated with thyroid hormone replacement, doses are increased initially by 0.025 mg. After initiation of therapy, doses are increased incrementally by 0.025 mg every 3 to 4 weeks until patients show improvement in their urticarial lesions. The authors' observations suggest that clinical changes or improvements are not seen until TSH levels are reduced to negligible or near-negligible levels; thyroid hormone and TSH levels are obtained before initiation of therapy and with any dosage adjustment. In the event of intolerable side effects or evidence of hyperthyroidism (clinically or by way of laboratory data), therapy is adjusted or, if the urticaria persists, discontinued. Once the lesions of CU begin to resolve, the dose of l-thyroxine is not increased unless there is a recurrence of disease. Ancillary pharmacologic agents such as H₁ or H₂ antihistamines, leukotriene modifiers, or oral steroids can be used if necessary to control refractory disease. The goal of therapy is complete resolution of hives, though near-complete resolution or even partial resolution would be grounds on which to continue treatment. After sustained improvement is seen (ie, after 3 to 6 months of treatment), gradual reduction and or discontinuation of l-thyroxine with careful monitoring of clinical and laboratory status can be considered. In the event of disease recurrence, treatment can be re-initiated at the lowest dose necessary to resolve further urticarial lesions from developing.

Summary

Though the usefulness of thyroid hormone therapy in patients who are euthyroid and have CU has not been demonstrated in a controlled trial and though the theories the authors propose for causation and resolution have yet to be proven, the authors' observations strongly suggest that CU in patients with autoimmune thyroid disease is the only situation in which the lesions of CU seem to resolve with the treatment of an underlying disease state. They suggest that this model is ideal for determining how low-grade autoimmunity may cause CU and allows specific experiments to be used to test the authors' hypothesis. l-Thyroxine is not advocated as a treatment of hives per se; rather it is a therapy that addresses an underlying autoimmune state affecting the thyroid gland. The authors look forward to the discovery of other markers of low-grade autoimmune disease that may give insight into alternative theories of pathophysiology and treatment responses. The challenge remains in identifying these markers.

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