

The thyroid and urticaria

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Purpose of review

Although it is generally accepted that thyroid autoimmunity is more prevalent in patients with chronic urticaria than in the general population, the importance of this finding is unclear. In addition, there are reports that chronic urticaria remits in some but not all patients who have evidence of thyroid autoimmunity and are treated with l-thyroxine. This review will summarize the history of this controversy and suggest a possible role for thyroid autoimmunity in the pathophysiology of chronic urticaria.

Recent findings

Important subsets of patients with chronic urticaria have autoantibodies to the high-affinity receptor for IgE (Fc ϵ RI), anti-IgE, and antithyroid antibodies. Patients with chronic urticaria and biochemical evidence of thyroid autoimmunity may have active thyroid disease or may be clinically euthyroid. These patients are often poorly responsive to conventional therapy of urticaria and may have more chronic disease. New findings on the pathogenic effects of anti-Fc ϵ RI autoantibodies and of antithyroid antibodies have revealed a role for complement activation.

Summary

Currently, there are no compelling arguments to decide whether or not thyroid autoimmunity plays a significant role in the pathogenesis of chronic urticaria. New developments concerning a role for complement activation in the pathogenesis of chronic urticaria may, however, lead to better understanding of this phenomenon in the future.

Keywords

anti-Fc ϵ RI, autoimmunity, thyroglobulin, thyroid peroxidase, thyroiditis, urticaria

Introduction

The pathophysiology of chronic urticaria is not completely understood, although most agree that the central event is activation of cutaneous mast cells. The lesions of chronic urticaria are characterized by a perivascular infiltrate that does not damage blood vessels and consists of CD4 and CD8-positive T lymphocytes, eosinophils, basophils and neutrophils [1,2]. In a substantial number of patients, complement-activating autoantibodies to the high-affinity receptor for IgE, Fc ϵ RI, are present [3]. The net result of activation of mast cells and influx of inflammatory cells is release or generation of multiple mediators, including histamine, prostaglandin D₂, leukotrienes C and D, platelet activating factor, anaphylatoxins (C3a, C4a, C5a), bradykinin, histamine-releasing factors, cytokines, and chemokines [4,5^{••}]. Patients with the daily occurrence of urticaria (hives) for at least 6 weeks are considered to have idiopathic urticaria [4]. Most patients (>95%) with chronic urticaria do not have an identifiable trigger such as contactants, ingestants, or physical stimuli and are considered to have chronic idiopathic urticaria [6]. Within this group, 35–50% of patients with chronic urticaria have functional complement-activating autoantibodies directed at the high-affinity receptor for IgE, Fc ϵ RI, or at IgE itself, and are said to have autoimmune chronic urticaria [5^{••},7,8[•]]. These patients tend to have worse disease, but this difference is not dramatic [5^{••},9–13].

Coexistence of skin diseases and thyroid autoimmunity

An increased prevalence of clinically important thyroid disease or subclinical thyroid autoimmunity has been noted in patients with chronic urticaria [14–19,20^{••}]. A similar phenomenon has also been reported in two other skin diseases with an autoimmune basis: alopecia areata and vitiligo [21–26].

Prevalence of thyroid autoimmunity in patients with alopecia areata or vitiligo

Du Vivier and Munro [21] measured thyroid autoimmunity in 60 patients with Down's syndrome and alopecia areata, comparing them with 23 patients without alopecia areata. The prevalence of thyroid autoimmunity in the patients with alopecia areata was 35% compared with 9% in the controls. Korkij *et al.* [22] performed a retrospective study of 38 patients with alopecia areata and 31 patients with vitiligo. They found antithyroid antibodies (anti-thyroglobulin or antithyroid peroxidase) in 29% of patients with vitiligo and 28% of patients with alopecia areata. No

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Abbreviations

Fc ϵ RI high-affinity receptor for IgE
TPO thyroid peroxidase

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control group was studied. Betterle *et al.* [23] conducted a case-controlled study of 3737 euthyroid patients, 373 of whom had vitiligo and 171 had alopecia areata. These were compared with 1000 patients with nonautoimmune diseases and 822 normal controls. Overall, they found a significant increase in thyroid autoimmunity in patients with vitiligo (11 versus 7%; $P < 0.05$) and alopecia areata (11 versus 7%; $P < 0.05$) compared with normals but not the nonautoimmune disease control group (9%). There did appear, however, to be a further increased prevalence of thyroid autoimmunity in males, but not females, with vitiligo (6%) or alopecia areata (9%) compared with the disease controls (2%) or the normals (1%), but this was not specifically addressed [23]. Handa and Kaur [25] retrospectively analyzed 1436 children with vitiligo and reported clinically significant thyroid disease in 0.5%. They did not look for evidence of subclinical thyroid autoimmunity and there was no control group. Nanda *et al.* [26] examined 80 consecutive children with alopecia areata and found that 14% had evidence of thyroid autoimmunity. Again there was no control group.

Prevalence of urticaria in patients with autoimmune thyroiditis

The earliest reports of urticaria in patients with thyroid autoimmunity were in patients with hyperthyroidism [27–29]. An association between hypothyroidism and chronic urticaria was noted in the 1980s although chronic urticaria occurs infrequently in patients with Hashimoto's thyroiditis [14,30,31].

Prevalence of thyroid autoimmunity in patients with chronic urticaria

Even though urticaria is a relatively rare manifestation of clinically apparent thyroid disease, an increased incidence of thyroid autoimmunity is found in patients with chronic urticaria. Approximately 5–34% of patients with chronic urticaria have antithyroid antibodies but are clinically and biochemically euthyroid [14–19,20^{••},32]. Another 5–10% have clinically apparent disease [14,19]. These antibodies are directed against thyroid peroxidase (TPO) or against thyroglobulin. These numbers need to be compared with the incidence of thyroid autoimmunity in the general population without known or former thyroid disease. The studies with the largest numbers are those of Leznoff *et al.* [14], who found that 5.6% of 477 control patients in a family practice had thyroid autoimmunity, and of Bjoro *et al.* [33], who reported an incidence of thyroid autoimmunity of 9.7% in a general Norwegian population. In the Leznoff study, no demographic information is available concerning the control group. In the Bjoro study, thyroid blood tests were routinely obtained only for those over the age of 40 and, given the increasing incidence of thyroid autoimmunity with age, may overestimate the true incidence of thyroid autoimmunity in adults. Other studies with

smaller control groups report an incidence of thyroid autoimmunity in controls ranging from 0 to 5% [17,19,34].

In the Leznoff study, of 624 patients with chronic urticaria, 90 (12.1%) were found to have thyroid autoimmunity. Of these, 46 (7.4%) did not have evidence of active thyroid disease [15]. In the Zauli study [19], of 122 patients, 55 (45%) were found to have thyroid autoimmunity. Of these, 41 (34%) were clinically euthyroid. Kikuchi *et al.* [35] prospectively examined 282 patients with chronic urticaria but did not state whether patients had clinical thyroid disease. They reported that 55 (19.5%) of their patients had evidence of thyroid autoimmunity with a preponderance of thyroid autoimmunity in patients with anti-FcεRI autoantibodies. They argued that the rate of thyroid autoimmunity in patients without anti-FcεRI autoantibodies was 10.9% – a number very similar to what might be expected in the general population. A prospectively enrolled, matched control group was not examined, however.

Toubi *et al.* reported a prospective study of 139 patients with chronic urticaria followed for 5 years and compared the incidence of thyroid autoimmunity with that of 60 age and sex-matched healthy adults [34]. The chronic urticaria population was a very ill group of patients, with 94% continuing to have chronic urticaria 6 months after enrollment in the study. The incidence of thyroid autoimmunity was 12% overall and the incidence of thyroid autoimmunity in euthyroid patients with chronic urticaria was 10.1%. Although this is similar to the figure reported by Leznoff and less than that reported by either Zauli or Kikuchi, the incidence of euthyroid thyroid autoimmunity in chronic urticaria in this study was much higher than that found in their control group (zero incidence; $P = 0.004$). These investigators report that the presence of thyroid autoimmunity in chronic urticaria predicts a longer duration of disease, with 52% of the thyroid autoimmunity-positive patients continuing to have chronic urticaria at 5 years compared with 16% of the thyroid autoimmunity-negative patients [34]. Verneuil *et al.* [36] studied 45 euthyroid patients with chronic urticaria, 32 patients with thyroid disease and thyroid autoimmunity, 22 patients with thyroid disease without thyroid autoimmunity, and 30 controls. The incidence of thyroid autoimmunity was higher in the chronic urticaria patients (27%) compared with controls (3%; $P < 0.01$). The presence of thyroid autoimmunity in patients with thyroid disease, however, did not predict the incidence of chronic urticaria (12.5% of those with thyroid autoimmunity versus 9% of those without thyroid autoimmunity). Turktaş *et al.* [17] reported an incidence of thyroid autoimmunity in euthyroid patients with chronic urticaria of 15% compared with the incidence of thyroid autoimmunity in an age, gender-matched control group of 5% ($P < 0.001$). Levy studied 187 children (age 7–17) referred for chronic

urticaria and found an incidence of thyroid autoimmunity of 4.3%, most of whom had overt thyroid disease. A prospective control group was not studied, but the incidence of thyroid autoimmunity in children is reported to be between 0.35 and 1.6% [37–39].

Thyroid autoimmunity and autoantibodies to FcεRI

Thyroid autoimmunity appears to occur more frequently in patients with other autoimmune skin diseases such as alopecia areata and vitiligo (see above) and in other nondermatologic immunologic diseases such as type I diabetes mellitus and Addison's disease [23,40,41]. For this reason, it is worthwhile considering that the presence of thyroid autoimmunity in patients with chronic urticaria is an epi-phenomenon. Kaplan [5•] observed that there is a positive association between the presence of thyroid autoimmunity and autoimmune chronic urticaria. He also noted, however, that there are many patients without anti-FcεRI antibodies who have thyroid autoimmunity but suggests that they occur at a rate similar to that expected in the general population. In this argument, the occurrence of thyroid autoimmunity in those chronic urticaria patients without anti-FcεRI antibodies is just by chance and the occurrence in those who are positive for anti-FcεRI autoantibodies is only another autoimmune activity in a patient with a predisposition to the production of autoantibodies [5•,35]. A similar conclusion was reached independently by Caproni *et al.* [42]. Recently, Fusari *et al.* [32] reported 82 patients with chronic urticaria, 29% of whom had thyroid autoimmunity. They found a positive autologous serum skin test (ASST) in 62% of chronic urticaria patients who had thyroid autoimmunity and in 39% of patients without thyroid autoimmunity. In this study, after 1 year of observation, 87% of the patients with thyroid autoimmunity continued to have a positive ASST compared with one of 13 patients without thyroid autoimmunity, even though the urticaria had resolved. Thus, it is generally agreed that there is an association between thyroid autoimmunity and the presence of anti-FcεRI autoantibodies but not that this is pathophysiologically important. It is also possible, however, that excess thyroid autoimmunity occurs in chronic urticaria patients who do not have anti-FcεRI autoantibodies, depending on the rate of thyroid autoimmunity in control groups. The presence of thyroid autoimmunity may be an independent risk factor for chronic urticaria, but this is unproven.

Treatment with thyroid hormone

There is evidence that treating patients who have both chronic urticaria and thyroid autoimmunity with exogenous thyroid hormone (levothyroxine) leads to significant improvement in their urticaria [15,16,18,43,44]. The dose of thyroid hormone given to each patient has not been standardized. Leznoff and Sussman [15] treated 46

patients who had idiopathic chronic urticaria and angioedema (ICUA) with l-thyroxine. Eight patients had an initial clinical response and six of these had a sustained response. Four of the six continually responsive patients had remissions and exacerbations of their hives as thyroid hormone was started and discontinued. Even though they stated that 'The patient in whom improvement in ICUA appeared to relate to l-thyroxine treatment were too few to be significant' [15] (p. 69) they recommended a 4–8-week trial of 150–200 µg/day in euthyroid patients. Rumblyrt *et al.* [16] reported seven euthyroid patients with chronic urticaria and thyroid autoimmunity and three control patients with chronic urticaria without thyroid autoimmunity, all of whom were treated with 25–100 µg of l-thyroxine daily. All seven patients with thyroid autoimmunity had a dramatic improvement in chronic urticaria whereas the three controls did not. L-thyroxine was stopped in five patients with return of symptoms and the symptoms again remitted with restarting of thyroid replacement therapy. In one patient, this pattern of thyroxine-associated remission of chronic urticaria was seen in a double-blind placebo-controlled challenge setting. A relationship between the extent of thyroid suppression and clinical response was not evaluated. Gaig *et al.* [44] treated 18 patients who had chronic urticaria and thyroid autoimmunity with l-thyroxine and reported good responses in 15 patients, partial responses in two patients and no response in only one patient. Again, this was not a blinded or placebo-controlled study.

Possible mechanisms

The biologic basis for a possible effect of l-thyroxine on the severity of chronic urticaria in patients with thyroid autoimmunity is unknown. Rumblyrt *et al.* [16,20•] proposed that an inflammatory response in the thyroid leads to a generalized inflammatory state and lowers the threshold of mast cells to other stimuli. In this scenario, suppression of the thyroid gland would decrease the recruitment of inflammatory cells and thus decrease the production of inflammatory mediators.

Another possible mechanism that could make a connection between thyroid autoimmunity and chronic urticaria is if there is an IgE response against the thyroid antigens. Concha *et al.* [45] tested this hypothesis by modifying commercial kits designed to identify IgG antibodies so that they could detect IgE antithyroid peroxidase (TPO) and antithyroglobulin. Only two of 20 patients (10%) had detectable levels of IgE antithyroid antibodies. Thus, although this mechanism may be extant in a few patients, it does not seem to be important in the majority.

Autoantibodies to FcεRI in patients with chronic urticaria, but not similar antibodies in controls, are thought

to activate the complement system, generating C5a and augmenting activation of cutaneous mast cells and basophils [5^{••}]. In a parallel observation, antithyroglobulin antibodies in autoimmune thyroid disease behave differently from similar antibodies in healthy individuals. The antibodies in patients with clinically significant thyroid disease tend to be directed against specific epitopes and to activate complement [46]. The antithyroid antibodies in euthyroid patients with chronic urticaria have not been evaluated in this fashion. Furthermore, TPO has been reported to bind C4 leading to complement activation [47]. Thus, for patients with either anti-FcεRI autoantibodies or antithyroid autoantibodies, there may be low levels of complement activation leading to mast cell activation. In susceptible patients, with antithyroid antibodies without anti-FcεRI antibodies, there may be a threshold at which point there is enough complement activation to precipitate chronic urticaria. In patients with both thyroid autoimmunity and anti-FcεRI autoantibodies, there may be a synergistic effect resulting in mast cell activation. In either of these situations, suppression of the thyroid gland could decrease the level of thyroid immune complexes by reducing the amount of antigen, thyroglobulin or TPO, leading to decreased levels of complement split products. This is a testable hypothesis.

Conclusion

Although it is generally accepted that the incidence of thyroid autoimmunity in euthyroid patients with chronic urticaria is greater than in control populations, the significance of this is uncertain. This is an important clinical question because of implications regarding treatment of these patients with l-thyroxine. At present, anecdotal evidence both supports and refutes the idea of prescribing l-thyroxine for euthyroid chronic urticaria patients who have thyroid autoimmunity. As outlined above, new findings concerning the role of complement in the pathophysiology of autoimmune urticaria and autoimmune thyroid disease may lead to identification of specific patients who can benefit from such therapy.

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