

Thyroid Autoimmunity in Chronic Idiopathic Urticaria

Implications for Therapy

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Abstract

The association between thyroid autoimmunity and chronic idiopathic urticaria has long been recognized, although prevalence rates differ in the studies reported to date (from 12 to 29%). There is, therefore, a strong indication to screen patients affected by chronic urticaria of unknown origin for thyroid antibodies (anti-thyroperoxidase and antithyroglobulin) and, when positive, for serum thyrotropin to assess thyroid functional status.

Less clear is the implication of thyroid autoimmunity for therapy, as most patients with urticaria who have associated thyroid autoimmunity are euthyroid. There is no doubt that cases with clinical or subclinical thyroid dysfunction should undergo treatment with either levothyroxine or antithyroid drugs for hypo- or hyperfunction, respectively. Although the best remission rates for symptoms of urticaria have so far been obtained with levothyroxine in patients who are euthyroid, monitoring of thyroid function through serum thyrotropin determination is highly recommended because of the risk of hyperthyroidism, especially in the elderly.

Chronic urticaria is currently defined as recurrent (almost daily) attacks of hives, accompanied by angioedema in 40 to 50% cases, of 6 or more weeks duration. For both the dermatologist and the allergist chronic urticaria is a common and complex condition, whose management is time consuming and is often not cost-effective.

Although there are several known causes of chronic urticaria (physical, vasculitic, allergic and contact are considered the most important causes), the etiology of quite a number of cases still remains elusive. These latter cases are commonly defined as chronic idiopathic urticaria.

A variable proportion (30 to 50%) of idiopathic cases has been recently assumed to be autoimmune. There is, in fact, growing evidence that the functional (i.e. capable of degranulating mast cells *in vitro* and/or *in vivo*) immunoglobulin (Ig) G anti- α subunit (extracellular domain) of the Fc ϵ receptor autoantibody, is responsible for the recurrent episodes of hives in these patients (for a review see Greaves^[1] and Kaplan^[2]). It has recently been shown that the antibody is directed against the unoccupied receptor. In up to 10% of cases antibodies against the α subunit of IgE have also been described. The ability of such autoantibodies to activate basophils and mast cells is increased in the presence of complement, probably via the formation of C5a (anaphylotoxin).^[3,4] Histologic examination of chronic idiopathic urticaria reveals a cellular infiltrate (CD3+ T lymphocytes) and cytokine

pattern (interferon- γ , interleukin-4 and -5) similar to that of allergen-induced late-phase reaction. However, both features are not significantly different in IgE receptor antibody-positive and -negative chronic idiopathic urticaria cases.^[5,6]

The reported efficacy of immunosuppressive (corticosteroids, cyclosporine) or immunomodulating therapies (plasmapheresis, intravenous immunoglobulin) in chronic idiopathic urticaria, is also in favor of an autoimmune pathogenesis. Unfortunately, randomized controlled studies in large populations are not yet available.^[2]

Indirect evidence in favor of the existence of autoimmune urticaria comes from the association of a proportion of these cases with thyroid autoimmunity. The frequency of thyroid autoantibodies varies in the series reported so far and thyroid function seems to be compromised in less than 50% of thyroid autoantibody-positive cases. Both autoimmune hypothyroidism and hyperthyroidism have been described, although the former appears to be far more common.^[7]

There is no evidence of a causal relationship between the two types of autoimmunity (receptor and thyroid) and, so far, they must be considered parallel phenomena.

Another point of uncertainty is whether the treatment of thyroid dysfunction (with either hormonotherapy or antithyroid drugs) is beneficial in the control of symptoms of urticaria, and also whether antibody-positive, but otherwise euthyroid patients,

should undergo therapy with levothyroxine (LT4) for the same purpose.

In the present review of the literature and of our own data we will, therefore, address the following issues:

- the prevalence of thyroid autoantibodies [antithyroperoxidase and thyroglobulin, antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG), respectively] and of thyroid autoimmune disease (autoimmune thyroiditis and Graves' disease) in chronic idiopathic urticaria
- the implications for therapy.

1. Thyroid Autoimmunity in Chronic Idiopathic Urticaria

The first report of an association between chronic idiopathic urticaria and thyroid autoimmunity was published by Leznoff and Sussman in 1983.^[8] They found thyroid microsomal antibody (TMA) in 12% of 140 patients and some years later^[9] in 14% of a larger series of similar cases. Other reports^[10-13] followed (table I).

More recent studies^[12,13] report figures of 20% for anti-TPO alone and 29% for any type of thyroid autoantibody (anti-TPO alone, anti-TG alone, anti-TPO associated with anti-TG). This discrepancy might, at least in part, be due to the different sensitivity of the methods used to detect thyroid autoimmunity.

In the 1980s the method used to detect TMA was either immunofluorescence or hemoagglutination, which may be less sensitive than the present methods to detect anti-TPO.

Additionally, some authors do not seem to have evaluated the prevalence of anti-TG, which can be found dissociated from anti-TPO in 5 to 23% of thyroid antibody-positive cases of chronic urticaria.^[10-12] In this context, recent work on the importance of anti-TG in the diagnosis of autoimmune thyroiditis is worth mentioning. Lindberg et al.^[14] studied sera from 141 children and adolescents for thyroid autoantibodies and found that radioimmunoassay-based anti-TG was the only test that identified autoantibodies in all cases of autoimmune thyroiditis.

In conclusion, the prevalence of positive thyroid antibodies reported by different groups is difficult to compare because of the different assays used and different cut-off values, but still the association is significant when compared with the general population, which ranges from 1 to 10% depending on age and sex (ageing and female gender being associated with the highest prevalences).^[15-17]

In most reports,^[8,10,12] thyroid dysfunction or altered serum thyrotropin levels are present in 40 to 54% of thyroid antibody-positive patients with urticaria and angioedema. The most frequent finding is hypothyroidism or elevated serum thyrotropin levels (subclinical hypothyroidism), whereas autoimmune hyperthyroidism (Graves' disease) or low serum thyrotropin levels is less frequent. Recently, we have re-evaluated (follow-up ranging

Table I. Prevalence of thyroid autoimmunity in chronic idiopathic urticaria

Reference	No. of urticaria cases	Any thyroid antibody-positive (% of patients)
Leznoff et al. ^[8]	140	17 (12)
Leznoff and Sussman ^[9]	624	90 (14)
Turktas et al. ^[10]	94	11 (12)
Gaig et al. ^[11]	170	25 (15)
Zauli et al. ^[12]	122	35 (29)
Ryhal et al. ^[13]	25	5 (20)

from 6 to 18 months) a group of 27 patients with chronic idiopathic urticaria and associated thyroid autoimmunity. Sixteen (11 females, five males) of these patients are still euthyroid with normal thyrotropin (59%), four females (15%) are being treated for Graves' disease with antithyroid drugs and seven (five females, two males) have high serum thyrotropin levels and are on therapy with LT4 (26%). All of the four patients with Graves' disease, besides having anti-TPO and/or anti-TG antibodies, were positive also for antithyrotropin-receptor antibodies. In the study of Gaig et al.^[11] Graves' disease was present in two out of 20 (10%) antibody-positive patients with urticaria. One would have expected a higher prevalence of Graves' disease in autoimmune urticaria, as both conditions represent models of antireceptor autoantibody-associated, or possibly -mediated, disease.

A few other anecdotal reports about the association between thyroid autoimmunity and chronic idiopathic urticaria can be found in the literature, but they do not provide prevalence rates.

Recently, following the report of one patient who was chronic idiopathic urticaria-positive for IgE anti-TPO,^[18] it has been hypothesized that IgE anti-TPO could cross-react with peroxidase-containing food (vegetables), whose ingestion would induce the appearance of hives. In this study, Tedeschi et al.^[19] tested for IgE antibodies to TPO in 23 patients who were chronic idiopathic urticaria-seropositive for IgG anti-TPO and found none of these patients were positive for IgE anti-TPO.

Interestingly, other autoantibodies (antinuclear, antismooth muscle, anticardiolipin, antineutrophil) that have been searched for so far, either have not been found to segregate with chronic idiopathic urticaria^[13] or, when found, have low titers^[20] and, therefore, are devoid of any significance. It seems as if chronic idiopathic urticaria should be classified more as an organ-specific autoimmune disease and should probably be investigated for other organ-specific autoimmune response (gastric, adrenal, islet cells autoantibodies).

In conclusion, there is now convincing evidence of a significant association between thyroid autoimmunity and urticaria, although the underlying mechanism is still far from clear. It is, however, still controversial whether screening for thyroid autoimmunity is advisable in all chronic idiopathic urticaria cases. In fact, while guidelines^[21] have been published by a joint task force

of allergists suggesting screening patients with chronic idiopathic urticaria, especially women, for both thyroid autoantibodies, a group of European dermatologists, in their recommendations for best practice in the assessment and diagnosis of chronic urticaria, do not mention these thyroid tests.^[22] An intermediate position has recently been assumed by Grattan et al.,^[23] who have prepared guidelines on behalf of the British Association of Dermatologists. They advocate that thyroid autoantibodies should be considered and thyroid function tests performed if thyroid dysfunction is likely. We interpret this to mean 'if there is either clinical evidence of frank dysthyroidism or a suggestive family history of autoimmune thyroid disease'.

2. Implications for Therapy

Firstly, it should be emphasized that clinical experience shows that chronic idiopathic urticaria can improve or remit spontaneously. The frequency of spontaneous remission is often difficult to assess, as the follow-up of patients with chronic idiopathic urticaria is not always an easy task. The frequency of spontaneous remission is, in fact, biased by a high drop-out rate, as these frustrated patients either seek the advice of other physicians (and also non-physicians) or simply give up or do not come back if they are free of symptoms.

However, in a recently published follow-up (1 to 3 years) of 220 adult patients, Kozel et al.^[24] reported a spontaneous remission rate of 47% in those cases in whom no cause of urticaria and/or angioedema could be identified. In this study, 16 euthyroid patients with chronic idiopathic urticaria and thyroid autoimmunity who had not receive LT4 treatment, had an even higher rate of spontaneous remission of urticaria after withdrawing all standard medications (mostly histamine H1 receptor blockers), with complete remission seen in nine patients (56%) and partial remission in two patients (12%).

Table II and table III summarize the literature and personal data on clinical responses of patients with euthyroid and dysthyroid chronic idiopathic urticaria and thyroid autoimmunity to treatment with either LT4 or antithyroid drugs (for Graves' disease).

In 1983 Leznoff et al.^[8] treated seven euthyroid patients with LT4 and obtained a partial to complete remission in five of them (71%) [table II]. Six years later, however, in the largest study published to date (patient inclusion criteria were clinical or sub-clinical hypothyroidism or severe urticaria), Leznoff and Sissman^[9] observed some beneficial effect in 17% of 46 patients. In the few responders, however, there was a marked improvement. Although it is difficult to determine from reading the paper whether the remission was obtained in euthyroid or dysthyroid cases.

Table II. Clinical response of euthyroid chronic idiopathic urticaria patients with thyroid autoimmunity

Reference	No. of euthyroid patients treated with LT4	Complete remission (% of patients)	Partial remission (% of patients)	No remission
Leznoff et al. ^[8]	7	3 (43)	2 (28)	2
Rumbyrt et al. ^[25]	7	7 (100)	0	0
Gaig et al. ^[11]	9	4 (44)	5 (56)	0

LT4 = levothyroxine.

Subsequently, Rumbyrt et al.^[25] reported a marked improvement of chronic hives within 4 weeks' of commencing treatment with low-dosage thyroxine in all seven euthyroid patients (table II). No adverse effects were reported.

Recently Gaig et al.^[11] reported an 95% partial to complete remission rate in a mixed population of patients with normal and altered (either high and low) thyrotropin values (table II and table III). Discontinuation because of adverse effects was very low (one case), although the median dosage to achieve a clinical benefit was fairly high (87.5 µg/day).

Our personal preliminary experience with 11 patients is less enthusiastic, as we observed some improvement in only 36% of patients who had been treated for either Graves' disease or a significant serum thyrotropin level increase (LT4 dosages ranging from 50 to 100 µg/day). As previously discussed, we have not treated patients with normal thyroid status with LT4 so far.

In all studies, the majority of patients with dysthyroidism, whether responders or non-responders to treatment in terms of their urticaria, had normalized their serum thyrotropin levels. Additionally, euthyroid patients treated with LT4 showed a reduction in serum thyrotropin level from the basal value. Of interest in this context, Padberg et al.^[26] found that prophylactic treatment of euthyroid patients with autoimmune thyroiditis with LT4 reduced both serological and cellular markers of autoimmune thyroiditis and suggested, therefore, that such treatment might be useful to stop the progression or even manifestation of the disease. Although long-term clinical benefit remains to be established, this study is reassuring, since it suggests that treating eu-

Table III. Clinical response of chronic idiopathic urticaria with thyroid autoimmune dysthyroidism to treatment with either substitute therapy (LT4) or with antithyroid drugs

Reference	No. of patients treated with LT4	No. of patients treated with antithyroid drugs	Complete remission (% of patients)	Partial remission (% of patients)	No remission (% of patients)
Gaig et al. ^[11]	9	2	6/11 (55)	4/11 (36)	1/11 (9)
Zauli ^a	7	4	3/11 (27)	1/11 (9)	7/11 (64)

a Unpublished observations.

LT4 = levothyroxine.

thyroid antibody-positive patients with LT4 is helpful for the underlying thyroid disease, if not for urticaria.

Overall, these data show that some improvement to complete remission of urticaria can be achieved in 17 to 100% of cases. There seems to be a euthyroid-hyperthyroid gradient in the rate of response of urticaria to therapy. In particular, the following conclusions can be drawn from the available data:

- there is a 71 to 100% remission rate (either partial or complete) of urticaria in patients with normal thyrotropin levels (euthyroid) treated with levothyroxine (table II)
- a 36 to 89% remission rate (either partial or complete) in patients with autoimmune hypothyroidism (both clinical and subclinical) and 50% with Graves' disease treated with thyroxine or antithyroid drugs, respectively (table III).

These conclusions, however, must be treated with caution, as they are drawn from non-randomized controlled studies in a limited number of cases. These patients differed from each other in terms of thyroid antibody titers, thyroid functional status, dosage of drugs received and severity of urticaria. Therefore, further investigations in this field are very welcome.

3. General Conclusions

Based on this literature review, the following tentative practical guidelines may be made for the evaluation and management of patients with urticaria after exclusion of known causes of urticaria:

- screening for serum thyroid antibodies and thyrotropin levels is strongly indicated, especially in women and in those with familiarity for thyroid autoimmune disease of any type
- hypothyroid (both clinical and subclinical) and hyperthyroid patients with urticaria should always be treated, irrespective of the efficacy of such treatment on urticaria symptoms, and subsequently followed-up by an endocrinologist. Also, either a high serum thyrotropin level or antithyroid antibody titre at baseline confers an increased risk of overt hypothyroidism of 2.6% per year and 2.1% per year, respectively^[17]
- euthyroid patients unresponsive to conventional therapy (H1 receptor blockers and/or corticosteroids) may be treated with low dosages (25 to 50 µg/day) of LT4, with careful monitoring of the clinical status and of serum thyrotropin levels, particularly in elderly patients. If no remission of urticaria is achieved within the first 4 to 8 weeks, LT4 should probably be withdrawn
- it is less clear whether the treatment should be discontinued, maintained or reduced in the patients who experience complete remission of their hives
- antibody-positive euthyroid patients, who either do not improve with LT4 or do not undergo therapy for any reason, should be strictly monitored with at least once a year testing of thyroid antibodies and thyrotropin level for the high probability of developing thyroid dysfunction.^[17]

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