

Resolution of chronic urticaria in patients with thyroid autoimmunity

Jeffrey S. Rumbyrt, MD, Joel L. Katz, MD, and Alan L. Schocket, MD

Denver, Colo.

Background: Autoimmune disease has been implicated as a cause of chronic urticaria, and anti-thyroid antibodies have been found in patients with chronic urticaria. Because some patients with chronic urticaria and autoimmune hypothyroidism have had clinical resolution with thyroid hormone replacement, we investigated the effect of thyroid hormone in euthyroid patients with chronic urticaria and thyroid autoimmunity.

Methods: Ten euthyroid patients with refractory hives were treated with thyroxine. Seven patients had elevated anti-thyroid antibodies at baseline. Thyroid function and anti-microsomal and anti-thyroglobulin antibody levels were monitored during treatment. If a clinical response was achieved, thyroxine was discontinued and restarted if symptoms recurred.

Results: Seven patients with elevated anti-thyroid antibodies reported resolution of symptoms within 4 weeks. Three patients without elevated anti-thyroid antibodies did not respond. Five patients had a recurrence of symptoms after treatment was stopped, which resolved after treatment was restarted. Thyroid-stimulating hormone levels decreased in all patients with a clinical response. No correlation between clinical resolution and anti-thyroid antibody levels was seen.

Conclusion: Thyroid autoimmunity in euthyroid patients may be associated with chronic urticaria, and treatment with thyroid suppression can result in clinical remission. (*J ALLERGY CLIN IMMUNOL* 1995;96:901-5.)

Key words: Chronic urticaria, thyroid autoimmunity, thyroid suppression

Chronic urticaria (CU), defined as recurrent episodes of hives with or without angioedema of at least 6 weeks' duration, is a common disorder for which the cause is rarely determined.¹ Although IgE-mediated mast cell degranulation with histamine release appears to be responsible for the symptoms of acute urticaria, different factors appear to be responsible for the lesions of CU. Histopathologic studies of the lesions of CU also reveal a different cellular pattern when compared with the lesions of acute urticaria. A perivascular accumulation of mononuclear cells, eosinophils, and mast cells²; the presence of activated CD4+ T cells within lesions³; and autoantibodies against

Abbreviations used

CU: Chronic urticaria
TA: Thyroid autoimmunity
TSH: Thyroid-stimulating hormone

the high-affinity IgE receptor in the serum⁴ have all been demonstrated in patients with CU. This suggests that autoimmunity may play a significant role in the pathogenesis of CU.

In 1983, Leznoff et al.⁵ described the association of CU and angioedema with thyroid autoimmunity (TA). Subsequently, they reported that six of 46 patients with CU and TA who were treated with thyroxine experienced a remission of symptoms. However, the selection criteria for treatment with thyroxine did not exclude patients with hypothyroidism.⁶ This study reports on seven euthyroid patients with CU and evidence of TA who had resolution of their symptoms after treatment with thyroxine. This suggests that TA is a cause of CU

From National Jewish Center for Immunology and Respiratory Disease Denver.

Received for publication Dec. 9, 1994; revised Mar. 8, 1995; accepted for publication Mar. 13, 1995.

Reprint requests: Jeffrey S. Rumbyrt, MD, Denver Allergy and Asthma Associates, P.C., 8805 West 14th Ave., Lakewood, CO 80215.

Copyright © 1995 by Mosby-Year Book, Inc.
0091-6749/95 \$5.00 + 0 1/164735

TABLE I. Thyroxine dosing, symptom resolution time, and medication requirements in euthyroid patients with CU and thyroid antibodies

Patient No.	Daily dose of T4 (mg)	Time required (wk)			Prestudy medications	Outcome
		1st R	Recurrence	2nd R		
1* (M, 36)	0.10-0.15	2	<1	3	Hydroxyzine, cyproheptadine, ranitidine, diphenhydramine, prednisone	Rare hives for >1 yr; T4, doxepin
2* (F, 33)	0.10-0.25	<2	2	2	H1, H2 blockers, prednisone	No hives for 7 mo; T4
3 (F, 32)	0.10	<2	<4	2	Prednisone, hydroxyzine, astemizole, doxepin, ranitidine	No hives for 8 mo; T4
4 (M, 66)	0.05	<2	None	—	Doxepin, famotidine, prednisone	Rare hives for >1 yr; hydroxyzine (prn only)
5 (F, 46)	0.25	<4	None	—	Hydroxyzine, prednisone	No hives for >1 yr
6† (F, 23)	0.125-0.187	<4	<2	<4	Hydroxyzine, astemizole, prednisone	No hives for 4 mo; T4, astemizole (prn only)
7† (F, 44)	0.10-0.20	2	1	2	Doxepin, ranitidine, hydroxyzine	No hives for >1 yr; T4

Each patient's age (in years) and sex are given in parentheses.

T4, Thyroxine; R, resolution; H1, H2 blockers, H1 and H2 histamine receptor blockers; prn, as needed.

*Patient required an increase in thyroxine dose after an initial response.

†Patient was receiving thyroxine at baseline and had dose increased.

and that treatment with thyroid suppression can result in clinical remission.

METHODS

All 10 patients were selected from a CU clinic at the National Jewish Center. Seven patients were selected sequentially on the basis of the presence of normal thyroid function and anti-microsomal and/or anti-thyroglobulin antibodies. Three control subjects were selected sequentially on the basis of the presence of normal thyroid function and no evidence of thyroid autoimmunity. CU was defined as described previously. All patients had previous evaluations that failed to identify a specific cause for their symptoms and had been treated with standard therapy, including H₁- and H₂-receptor blocking agents, as well as oral corticosteroids, with inadequate clinical response.

Patients were evaluated for TA with tests for thyroid function (thyroxine and thyroid-stimulating hormone [TSH]) and for the presence of anti-thyroid antibodies (anti-thyroglobulin and anti-microsomal). Criteria for the diagnosis of TA included anti-thyroglobulin levels greater than 1.0 U/ml or titers greater than 1:240 and/or anti-microsomal antibody levels greater than 0.3 U/ml or titers greater than 1:240. Antibody levels were determined by ELISA, and antibody titers were determined by hemagglutination. Normal (euthyroid) ranges of thyroxine and TSH were 4.5 to 12 µg/dl and 0.5 to 6.2 mIU/ml, respectively. Patients with laboratory or clinical

findings suggestive of hyperthyroidism or hypothyroidism were excluded from the study.

Patients began receiving doses of thyroxine that ranged from 0.025 mg to 0.1 mg per day, depending on their age and baseline medical condition. Two patients receiving thyroid replacement therapy with normal thyroid function had their doses increased. A clinical response was defined as elimination of daily spontaneous hives, a reduction in the frequency of daily spontaneous hives, or a reduction in the need for regular or as-needed medication to control daily spontaneous hives. Symptom reports and medication requirements were obtained from the patients themselves. If or when a clinical response was achieved, thyroxine therapy was discontinued and restarted (at the same dose) if symptoms recurred. If a given dose of thyroxine was ineffective in achieving a clinical remission, the dose was increased. Thyroid function and anti-thyroid antibody tests were repeated at 4 to 6 weeks after therapy was initiated or after the dose was changed. A single patient underwent a double-blind trial with thyroxine and placebo. All patients were followed up for a minimum of 12 weeks.

RESULTS

Seven patients with CU and TA and three patients with CU alone began receiving thyroxine. The data for the patients with CU and TA are shown in Table I. The average age of the patients

TABLE II. Thyroid function and anti-thyroid antibody levels in patients with CU before and after treatment with thyroxine

Patient No.	T4/TSH baseline	T4/TSH with thyroxine	AT/AM baseline	AT/AM with thyroxine
1	5.8/2.73	6.0/0.76	10.5/6.0	47.9/25.3
2	7.8/6.1	10.9/0.4	inc/inc*	nl/inc*
3	6.5/2.2	9/0.06	3.4/16.7	2.2/9.6
4	6.9/2.79	7.8/1.93	2.2/1.7	3.5/1.6
5	7.9/0.89	ND	nl/inc ¹	ND
6†	5.7/4.98	ND	228.4/3.3	ND
7†	8.4/1.13	15.7/<0.05	6.6/256	3.8/116.6
8 (M, 52)	6.0/1.0	7.8/0.8	<0.5/<0.5	<0.5/<0.5
9 (F, 44)	10.5/0.6	10.8/0.5	0.7/0.3	0.8/0.3
10 (F, 51)	6.3/2.09	7.9/0.21	<0.5/<0.5	<0.5/<0.5

Patients 1 to 7 have CU and TA. Patients 8 to 10 had CU without TA and are referred to in the text as control subjects.

T4, Thyroid hormone level; AT, anti-thyroglobulin antibody level; AM, anti-microsomal antibody level; inc, increased; nl, normal value; ND, not done.

*Studies performed at outside laboratory reported as antibody titers.

†Patient was receiving thyroxine at baseline.

Normal levels: T4, 4.5-12 µg/dl; TSH, 0.5-6.2 mIU/ml; anti-thyroglobulin antibodies, <1.0 U/ml; anti-microsomal antibodies, <0.3 U/ml.

was 43 years, with a range of 23 to 66 years. Three patients were men, and seven were women. Six of 10 patients started therapy with a dose of thyroxine of 0.1 mg per day, and two other patients started therapy with doses of 0.025 mg and 0.05 mg, respectively. Two patients who were already taking thyroxine had their doses increased; one patient from 0.1 mg to 0.25 mg, and the other from 0.125 mg to 0.187 mg daily. Both of these patients had been previously diagnosed with hypothyroidism.

Thyroxine, TSH, and anti-thyroid antibodies were measured before and after treatment was initiated (Table II). For the seven patients with CU and TA, the average thyroxine level before starting treatment with thyroxine was 7.0 µg/dl (range, 5.7 to 8.4 µg/dl), and the average TSH level was 2.97 mIU/ml (range, 0.89 to 6.10 mIU/ml). For the three patients with CU alone, the average thyroxine level was 7.6 µg/dl (range, 6.0 to 10.5 µg/dl), and the average TSH level was 1.23 mIU/ml (range, 0.6 to 2.09 mIU/ml). Thyroid antibodies were measured directly in eight patients and reported as hemagglutination titers in two patients. With the exception of one normal anti-thyroglobulin titer in patient no. 5, all antibody levels or titers were increased at baseline (except in the three control subjects). None of the patients had laboratory or clinical features that suggested a noneuthyroid state before they began receiving thyroxine.

All seven patients with TA had dramatic improvement in their symptoms within 4 weeks of

starting thyroxine therapy. Three patients had relief in less than 2 weeks. The three patients without TA did not respond. All patients tolerated the dose of thyroxine on which they started. After a minimum of 4 weeks of treatment, thyroxine was discontinued in the patients who responded, and five patients had a recurrence of their urticaria within 4 weeks. Two patients did not have a substantial recurrence and have remained in remission since the cessation of therapy for a period of longer than 1 year. In the five patients whose symptoms recurred, thyroxine was restarted, and all five had resolution of their symptoms within 4 weeks. Two patients required an increased amount of thyroxine before complete resolution of symptoms was achieved. During treatment, the average thyroxine level increased to 9.9 µg/dl (range, 6.0 to 15.7 µg/dl), and the average TSH fell to 0.64 mIU/ml (range, <0.05 to 1.93 mIU/ml) for the patients with TA who had follow-up testing. Two patients did not have their thyroid function or thyroid antibody levels reassessed after thyroxine administration was restarted. For the patients without TA, the average thyroxine level increased slightly to 8.8 µg/dl (range, 7.8 to 10.8 µg/dl), and the average TSH level decreased to 0.5 mIU/ml (range, 0.21 to 0.8 mIU/ml). The antibody levels in these three patients did not change.

There was no consistent correlation between anti-thyroid antibody levels and clinical response. Of the four patients who had repeat antibody testing, two had a decrease in their anti-thyroglob-

ulin antibodies and two had an increase. Three patients had a decrease in their anti-microsomal antibodies, and one had an increase. Changes in the antibody levels for patient no. 2 could not be adequately assessed because they were reported as titers.

Interestingly, one patient (no. 1) underwent a double-blind trial with thyroxine and placebo. He had no symptoms while receiving thyroxine but had a recurrence of urticaria within 3 days of the start of placebo administration. Thyroxine was restarted, and his symptoms resolved in less than 3 weeks. He has since been free of symptoms.

DISCUSSION

CU is a clinical syndrome in which a variety of factors may play a role. Unfortunately, the agent or agents responsible for triggering this condition are determined in less than 30% of patients.⁷ It has been established that the pathophysiology of CU involves increased histamine and mediator release from mast cells⁸; other possible contributors include an increase in cutaneous histamine-releasing factor,⁹ and/or an alteration in histamine metabolism.¹⁰

Autoimmune disease has long been implicated in CU in both adults and children.^{11, 12} Whether through immune complex formation or deposition, complement activation, or the release of proinflammatory mediators from activated T cells, autoantibodies may play a role in perpetuating the inflammatory changes seen in CU. In addition, autoantibodies have been implicated as inducers of histamine release in basophils and skin mast cells in patients with CU, though the precise epitopes to which they bind have not been identified.⁴ This leads to speculation, moreover, that suppression of their production or inhibition of their action may play a potential therapeutic role.

The prevalence of anti-thyroid antibodies in the general population has been estimated at 3% to 6%,¹³ and they are commonly found in association with other autoimmune conditions, such as pernicious anemia and vitiligo.⁶ Because they have also been found, in one study, to occur in as many as 14% of patients with CU and because patients with CU and autoimmune hypothyroidism have had clinical resolution of symptoms with thyroid hormone replacement,⁶ we were led to investigate the role that thyroid hormone would play in euthyroid patients with CU and evidence of TA.

Ten euthyroid patients with CU unresponsive to conventional therapy were treated with thyroxine. Seven had elevated anti-microsomal and/or anti-

thyroglobulin antibodies, and three did not. Thyroxine therapy was initiated in eight patients and increased in two patients already being treated for hypothyroidism. Their data are included because they met our criteria of being euthyroid with refractory hives. In all seven patients with CU and TA, disease activity decreased within 4 weeks of initiating treatment, and in five cases, symptoms recurred after thyroxine administration was stopped. Furthermore, when treatment was restarted, clinical resolution occurred within 4 weeks, though two patients required an increase in dose. These observations clearly demonstrate the effectiveness of thyroxine treatment for our patients with CU and TA.

No patient withdrew from the study because of side effects, but one patient had laboratory data suggestive of hyperthyroidism after her thyroxine dose was increased (patient no. 7, thyroxine, 15.7 $\mu\text{g}/\text{dl}$; TSH, <0.05 mIU/ml). Interestingly, this patient was one of two already being treated with thyroxine for hypothyroidism who required an increased dose to suppress her hives. The other patient with hypothyroidism refused further testing. Two other patients had their TSH levels fall outside the normal range with treatment but had normal thyroxine levels and demonstrated no clinical signs of hyperthyroidism. Nonetheless, this underscores the necessity of periodic thyroid function testing, especially in patients who have clinical signs of hyperthyroidism or who may not tolerate elevated thyroxine levels.

Though it was originally believed that the anti-thyroid antibodies themselves were responsible for lesions seen in these patients, our observations suggest that the antibodies only serve as an indicator of autoimmunity because their levels do not correlate with disease activity. Because our observations also suggest that a decrease in TSH does correlate with disease activity, we propose that a potential mechanism responsible for the clinical improvement seen in our patients is the suppression of chronic thyroid stimulation and glandular inflammation. We further propose that the factors responsible for and generated from the recruitment of inflammatory cells (i.e., proinflammatory cytokines, histamine-releasing factors, autoantibodies) could not only perpetuate a chronic inflammatory state but could also decrease the mast cell threshold to endogenous peptides or exogenous allergens or stimulants (medication, infection, food, physical factors, etc.). Treatment with thyroxine decreases thyroid gland stimulation through negative feedback on the pituitary gland and reduction of TSH.

Though this mechanism is speculative, we believe that the production of autoantibodies is indicative of a heightened immunologic response, which may influence the development and/or persistence of CU. Moreover, we agree with the recommendations of Leznoff and Sussman⁶ that thyroid testing, including measurement of anti-thyroid antibodies, should be routinely considered in patients with CU refractory to standard therapy and that treatment with thyroid suppression be considered in patients with severe urticaria and evidence of TA despite a euthyroid state.

REFERENCES

1. Kaplan AP. Urticaria and angioedema. In: Middleton E Jr, Reed CE, Ellis EF, eds. *Allergy: principles and practice*. 3rd ed. St Louis: CV Mosby, 1988:1377-401.
2. Nabotny SF, Philips ME, Elias JM, Godfrey HP, Kaplan AP. Histologic studies of chronic idiopathic urticaria. *J ALLERGY CLIN IMMUNOL* 1983;71:177-83.
3. Mekori YA, Giorno RC, Anderson P, Kohler PF. Lymphocyte subpopulations in the skin of patients with chronic urticaria. *J ALLERGY CLIN IMMUNOL* 1983;72:681-4.
4. Hide M, Francis DM, Grattan CEH, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993;328:1599-604.
5. Leznoff A, Josse RG, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol* 1983;119:636-40.
6. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J ALLERGY CLIN IMMUNOL* 1989;84:66-71.
7. Quaranta JH, Rohr AS, Rachelefsky GS, et al. The natural history and response to therapy of chronic urticaria and angioedema. *Ann Allergy* 1989;62:421-4.
8. Kaplan AP. Urticaria: the relationship of duration of lesion to pathogenesis. *Allergy Proc* 1990;11:15-8.
9. Claveau J, Lavoie A, Brunet C, Bedard P-M, Hebert J. Chronic idiopathic urticaria: possible contribution of histamine-releasing factor to pathogenesis. *J ALLERGY CLIN IMMUNOL* 1993;92:132-7.
10. Kanny G, Moneret-Vantrin DA, Schohn H, Feldmann L, Mallie JP, Gueant JL. Abnormalities in histamine metabolism in chronic urticaria [Abstract]. *J ALLERGY CLIN IMMUNOL* 1994;93:222.
11. Harris A, Twarog FJ, Geha RS. Chronic urticaria in childhood: natural course and etiology. *Ann Allergy* 1983;51:161-5.
12. Small P, Barrett D, Champlin E. Chronic urticaria and vasculitis. *Ann Allergy* 1982;48:172-4.
13. Tunbridge WM, Evered DC, Hall K. The spectrum of thyroid disease in a community: the Wickham survey. *Clin Endocrinol* 1977;7:481-93.

AVAILABLE NOW! The FIVE-YEAR (1986-1990) CUMULATIVE INDEX TO THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY can be purchased from the Publisher for \$48.00. This comprehensive, 188-page reference guide is a current presentation of all topics included in the JOURNAL from January 1986 to December 1990 (volumes 77-86). It incorporates complete references to over 1500 original articles, abstracts, case reports, letters, editorials, and CME articles. It features 1662 subject headings, under which there are 5863 entries. Each subject entry lists the complete article title, author(s), volume, page, and year of publication. It also includes 5801 author entries, listing contributors, along with their respective titles, author-to-author referral, volume, page, and publication date.

To purchase, call or write: Mosby, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318, or telephone FREE, Subscription Services, 1 (800) 453-4351 or 314-453-4351. PREPAYMENT REQUIRED. Make checks payable to Mosby. (All payments must be in US funds drawn on a US bank.) Price: \$48.00 in the US, \$54.35 in Canada, and \$51.00 international (price includes mailing charges).