

Clinical trial

The effect of L-thyroxine treatment on chronic idiopathic urticaria and autoimmune thyroiditis

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Abstract

Autoimmune thyroiditis (AT) is more prevalent in patients with chronic idiopathic urticaria (CIU) than in the general population. Previous small studies without any controlled comparison reported that CIU remits in patients with CIU and AT treated with L-thyroxine. To determine whether L-thyroxine treatment can improve the clinical course of CIU in patients with the co-occurrence of AT and CIU. A total of 749 patients with CIU were retrospectively studied. Clinical and laboratory evaluation and classification of chronic urticaria were performed according to the EAACI/GA(2)LEN/EDF/WAO guidelines. After L-thyroxine treatment for 53 ± 19 days, euthyroidism was restored in all subjects. Urticaria activity score (UAS) was evaluated at baseline and after three and six months. The control group consisted of matched 44 euthyroid subjects with CIU. A total of 44 (5.9%) patients were diagnosed to have hypothyroidism related to AT. Autologous serum skin test (ASST) was found to be positive in 17 (38.6%) of them. There was no statistically significant difference in baseline UAS, between the ASST+ (3.94 ± 1.52) and the ASST- (3.63 ± 1.42 ; $P = 0.27$) hypothyroid subjects and the euthyroid CIU controls (3.73 ± 1.74). During the L-thyroxine treatment, a significant reduction of UAS was observed in both hypothyroid ASST+ and ASST- subjects. However, the mean UAS after three and six months of L-thyroxine treatment remained not significantly different from that in control euthyroid subjects with CIU. L-Thyroxine treatment has no effect on the course of CIU in patients with CIU and AT.

Introduction

It is commonly accepted that thyroid autoimmunity is more prevalent in patients with chronic idiopathic urticaria (CIU) than in the general population.¹⁻³ Thyroid autoimmunity appears to be more frequent in patients with CIU and a positive autologous serum skin test (ASST) than in those with a negative ASST.⁴ In addition, there is a positive correlation between antithyroid peroxidase (anti-TPO) antibodies and anti-immunoglobulin (Ig) E receptor antibodies.⁵

In addition, there are some reports that CIU remits in some patients who have evidence of thyroid autoimmunity and are treated with L-thyroxine.^{6,7} In another study, treatment with L-thyroxine did not improve CIU, but a few patients demonstrated a dramatic response.⁸ However, there are no double-blind placebo-controlled studies of L-thyroxine treatment in patients with CIU with anti-TPO antibodies with or without thyroid dysfunction. Moreover, for hypothyroid patients with CIU, a randomized double-blind placebo-controlled study would be difficult to justify ethically. Therefore, we undertook a

retrospective study to determine whether L-thyroxine treatment can improve the clinical course of chronic urticaria in patients with the co-occurrence of autoimmune thyroiditis (AT) and CIU.

Materials and methods

Subjects

The cases of patients referred to the outpatient allergy clinic from the Ashdod region (Israel) between May 2003 and April 2010 because of a diagnosis of CIU and/or angioedema for at least six weeks were retrospectively collected. Only subjects with chronic spontaneous urticaria were included. Exclusion criteria were any type of physical urticaria, cholinergic urticaria, contact urticaria, and food- and drug-induced urticaria.

We routinely check thyroid-stimulating hormone (TSH), thyroid hormones, antithyroglobulin, and anti-TPO antibodies in CIU, and if hypothyroidism with positive thyroid autoimmunity is diagnosed, the patient undergoes further diagnostic work-up for diffuse thyroid hyperplasia, including thyroid scintigraphy and sonography, and begins L-thyroxine treatment. Each patient with CIU is followed monthly to assess any changes in their

urticaria, while being advised to use oral antihistamine medications in conventional doses daily.

Forty-four patients with CIU and with clinically hypothyroid AT were retrieved from our computerized database and enrolled into the study. Forty-four age- and sex-matched euthyroid CIU patients (without AT) from the same outpatient allergy clinic were randomly selected and included in the control group.

As part of the standard practice in our allergy clinic, all subjects had been informed about any risks involved with testing, and written informed consent for allergologic work-up [skin-prick test, autologous serum skin test (ASST)] had been obtained. As the above-mentioned laboratory work-up and ASST are part of routine diagnostic practice in our clinic, further ethical approval was not required.

Methods

Clinical evaluation of chronic urticaria

Clinical and laboratory evaluation and classification of chronic urticaria were performed according to the EAACI/GA(2)LEN/EDF/WAO guidelines.⁹

ASST was performed with 50 µl of the patient's undiluted serum after blood centrifugation, which was then injected intradermally into the volar aspect of the forearm together with simultaneously injected controls, including saline and 10 µg/ml histamine. The mean diameters of the wheals were measured at 30 minutes. The test was considered to be positive if the serum-injected site manifested a wheal with a diameter at least 1.5 mm greater than that of the saline.

Assessment of urticaria severity

A unified and simple scoring system, the urticaria activity score (UAS), according to the EAACI/GA(2)LEN/EDF/WAO guidelines was used to assess CIU clinical severity.⁹ Use of the UAS facilitates comparison of study results from different centers. The UAS is based on the assessment of key

urticaria symptoms (weals and pruritus) – graded from 0 (none) to 3 (severe).⁹ UAS is suitable for the evaluation of disease activity by patients with urticaria and their treating physicians.

Statistical analysis

Results are presented as mean ± standard deviation. Descriptive statistics were used to describe the demographic data and UAS. Comparability of demographic and baseline characteristics among study groups was assessed using the chi-square test, and a $P < 0.05$ was considered significant. All statistical analyses were performed using the software Statistica 6 (StatSoft Inc., Tulsa, OK, USA).

Results

During the study period, 749 patients with CIU were referred to our allergy clinic. Forty-four (5.9%) patients had a diagnosis of hypothyroidism related to AT. Demographic characteristics of the subjects are given in Table 1.

ASST was found to be positive in 17 (38.6%) of them. The subjects were characterized by low thyroid hormone levels ($P < 0.001$), high TSH ($P < 0.001$), and positivity for at least one autoantibody against the thyroid gland ($P < 0.001$) when compared with those of the control group, which consisted of 44 euthyroid subjects with CIU (Table 2).

There were no differences in duration/dosing of antihistamine therapy between the study groups, and the H₁ antihistamines' consumption was similarly decreased in all groups over the observational period.

As shown in Table 3, there was no statistically significant difference in baseline UAS, between the ASST+ (3.94 ± 1.52) and the ASST– (3.63 ± 1.42 ; $P = 0.27$) hypothyroid subjects and the euthyroid CIU controls

Table 1 Demographic and laboratory data of study groups

Characteristics	CIU ASST+ $n = 17$	CIU ASST– $n = 27$	Controls $n = 44$	P^a	P^b	P^c
Sex, female	15 (92.6%)	26 (94.1%)	40 (90.9%)	0.76	0.94	0.63
Age, years	45.2 ± 7.1	43.9 ± 9.4	42.7 ± 9.2	0.91	0.48	0.84
Body mass index, kg/m ²	27.9 ± 3.7	27.4 ± 3.5	26.9 ± 4.1	0.94	0.39	0.28
Thyroid-stimulating hormone (0.35–4.94 mIU/l)	22.7 ± 9.2	24.9 ± 5.4	2.6 ± 1.1	0.79	<0.001	<0.001
Free thyroxine (9–19 pmol/l)	9.4 ± 1.7	9.1 ± 1.5	14.3 ± 2.1	0.84	<0.001	<0.001
Antithyroid peroxidase antibodies, n (%)	25 (92.6%)	14 (82.4%)	2 (4.5%)	0.18	<0.001	<0.001
Antithyroglobulin antibodies, n (%)	18 (66.6%)	13 (76.4%)	1 (2.2%)	0.25	<0.001	<0.001

^a P value between CIU ASST+ and CIU ASST– groups; ^b P value between CIU ASST+ and control groups; ^c P value between CIU ASST– and control groups.

ASST, autologous serum skin test; CIU, chronic idiopathic urticaria; CIU ASST+, the cases of CIU patients with hypothyroidism and positive ASST; CIU ASST–, the cases of CIU patients with hypothyroidism and negative ASST; Controls, (control group) the cases of randomly selected euthyroid CIU patients.

Table 2 Demographic and laboratory data of control group

Characteristics	Control ASST+ <i>n</i> = 15	Control ASST- <i>n</i> = 29	<i>P</i>
Sex; female	14 (93.3%)	26 (89.7%)	0.46
Age, years	41.8 ± 10.7	43.5 ± 9.1	0.97
Body mass index, kg/m ²	27.2 ± 3.9	26.6 ± 4.3	0.91
Thyroid-stimulating hormone (0.35–4.94 mIU/l)	2.8 ± 0.9	2.4 ± 1.3	0.39
Free thyroxine (9–19 pmol/l)	13.7 ± 2.4	14.8 ± 1.9	0.94
Anti-thyroid peroxidase antibodies, <i>n</i> (%)	1 (6.7%)	1 (3.5%)	0.17
Antithyroglobulin antibodies, <i>n</i> (%)	0	1 (3.5%)	0.09

P value between ASST+ and ASST- euthyroid chronic idiopathic urticaria patients.

ASST, autologous serum skin test; control (control group), the cases of randomly selected euthyroid chronic idiopathic urticaria patients.

Table 3 Urticaria activity score in study groups and TSH levels in hypothyroid patients during the observational period

Characteristics	CIU ASST+ <i>n</i> = 17	CIU ASST- <i>n</i> = 27	Controls <i>n</i> = 44	<i>P</i> ^a	<i>P</i> ^b	<i>P</i> ^c
UAS at baseline	3.94 ± 1.52	3.63 ± 1.42	3.73 ± 1.74	0.27	0.21	0.39
UAS at 3 months	2.12 ± 1.17	2.26 ± 1.43	2.23 ± 1.22	0.96	0.16	0.93
UAS at 6 months	1.35 ± 1.32	1.37 ± 1.42	1.34 ± 1.18	0.68	0.82	0.65
TSH at baseline	22.7 ± 9.2	24.9 ± 5.4	2.6 ± 1.1	0.79	<0.001	<0.001
TSH at 3 months	3.7 ± 1.5	3.4 ± 1.7		0.28		
TSH at 6 months	2.9 ± 1.4	2.8 ± 1.7		0.34		

^a*P* value between CIU ASST+ and CIU ASST- groups; ^b*P* value between CIU ASST+ and control groups; ^c*P* value between CIU ASST- and control groups.

ASST, autologous serum skin test; CIU, chronic idiopathic urticaria; CIU ASST+, the cases of CIU patients with hypothyroidism and positive ASST; CIU ASST-, the cases of CIU patients with hypothyroidism and negative ASST; controls (control group) the cases of randomly selected euthyroid CIU patients; TSH, thyroid-stimulating hormone; UAS, urticaria activity score.

(3.73 ± 1.74). After L-thyroxine replacement treatment for 53 ± 19 days, euthyroidism (TSH <4.5 mIU/l) was restored in all subjects. During the treatment, a significant reduction of UAS was observed in both hypothyroid ASST+ and ASST- subjects. However, the mean UAS after three and six months of L-thyroxine treatment remained not significantly different from that in control euthyroid subjects with CIU (Fig. 1).

Discussion

The study shows that both ASST+ and ASST- hypothyroid patients with CIU and AT, treated with L-thyroxine, experience a similar clinical improvement of CIU. However, the comparable improvement of CIU severity was seen in euthyroid CIU patients without AT during the same period of the study. Therefore, we could speculate that an observed improvement of CIU severity was associated with the spontaneous remission of CIU and was not related to L-thyroxine treatment. In general, such spontaneous remission of CIU is reasonable and well recognized from several epidemiological studies.^{10,11}

Previous investigators detected a similar improvement in urticaria with normalization of thyroid function.^{12,13} They also observed a poor response to antihistamines and corticosteroids, without correction of the thyroid dysfunction. Nevertheless, in the absence of any controlled comparison in these studies, it is difficult to be certain whether L-thyroxine treatment was beneficial or whether there was a natural improvement of CIU.

The association of CIU with autoimmune thyroid disease has frequently been reported in adult populations, with the prevalence ranging from 14% to 33%.^{14,15} The mechanism whereby thyroid autoimmunity is associated with CIU is poorly understood. In a series of patients with CIU, only patients with chronic urticaria and Hashimoto thyroiditis had anti-Fcε RI antibodies in their sera that could induce degranulation of normal basophils.¹⁶ Even though skin biopsy specimens from patients with CIU, with or without Hashimoto thyroiditis, were indistinguishable by light microscopy, and no immune complex deposition was observed.¹⁶ Nevertheless, clustering of thyroid antimicrosomal antibodies was found in patients with a positive ASST, indicating the presence of

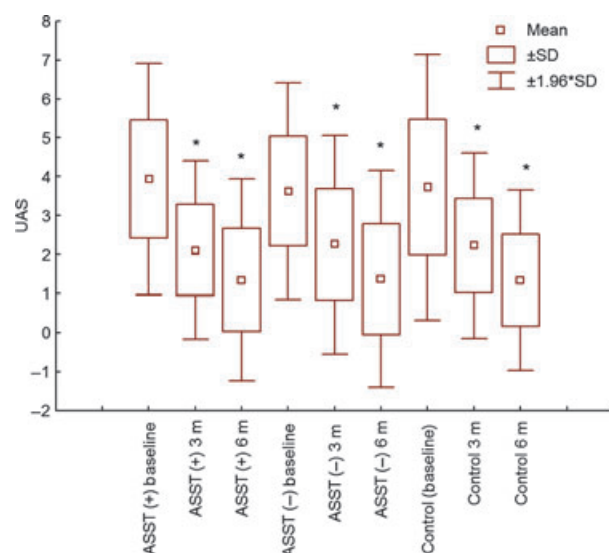


Figure 1 UAS changes in study groups. ASST, autologous serum skin test; UAS, urticaria activity score. ASST (+), chronic idiopathic urticaria + autoimmune thyroiditis patients, with positive ASST. ASST (-), chronic idiopathic urticaria + autoimmune thyroiditis patients, with negative ASST. Control, euthyroid patients with chronic idiopathic urticaria. 3 m, 3 months; 6 m, 6 months. * $P < 0.05$

functional histamine-releasing autoantibodies.¹⁷ It is well accepted that euthyroid patients with a positive anti-TPO antibody have a considerable risk of progression to hypothyroidism.¹⁸ Therefore, annual assessment of thyroid function in patients with CIU and increased antithyroid titers is recommended.¹⁹ Nevertheless, the epitopic cross-reactivity does not explain the increased prevalence of AT found in patients with CIU, and the frequent co-occurrence of AT and CIU likely reflects a genetic tendency toward autoimmune diseases.²⁰

In conclusion, our study does not support previous observations that in hypothyroid patients with CIU and AT, L-thyroxine treatment could improve the clinical course of CIU. We understand that the study has some limitations, while the main limitation is related to its retrospective nature with possible recording bias. Well-designed prospective studies are needed to clarify a role for L-thyroxine treatment in patients with CIU and AT.

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