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Chronic urticaria and thyroid pathology

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ABSTRACT

Urticaria is defined as the sudden appearance of erythematous, itchy wheals of variable size, with or without angioedema (AE) (swelling of the deeper layers of the skin). Its classification depends on time course of symptoms and the presence of eliciting factors. When it lasts less than 6 weeks it is classified as acute urticaria (AU), and if the symptoms persist for more than 6 weeks, it is classified as chronic urticaria (CU). Current International Guidelines also classify CU as chronic spontaneous urticaria (CSU) and inducible urticarial, according to the absence or presence of environmental triggering factors. CSU is defined as urticaria and/or angioedema in which there is no evidence of a specific eliciting factor. CSU is associated with autoimmunity in 30–45% of the cases, sharing some immunological mechanisms with other autoimmune diseases, and is associated with autoimmune thyroid disease (ATD) in about 4.3%–57.4% patients. Several studies suggest that adequate therapy with *anti*-thyroid drugs or levothyroxine in early stages of ATD and CSU, may help to remit the latter; but there is still a lack of double-blind, placebo-controlled studies that support this hypothesis in patients without abnormal thyroid hormone levels. The objective of this review is to describe the pathophysiology of chronic spontaneous urticaria and its association with autoimmune thyroid disease.

Keywords: Autoimmunity, Chronic urticaria, Histamine, Levothyroxine, Urticaria, Thyroid disease

INTRODUCTION

Urticaria is defined as the sudden appearance of erythematous, itchy wheals of various sizes, with or without angioedema (AE) (swelling of the deeper layers of the skin), that disappear without any trace in less than 24 hours.[1] In 40% of cases, it can occur simultaneously with AE, while in about 10% it manifests as AE alone.[2]

Urticaria is classified depending on time course of symptoms and the presence of eliciting physical triggers. When the symptoms last for less than 6 weeks it is classified as acute urticaria (AU), while chronic urticaria (CU) is the occurrence of symptoms for more than 6 weeks.[3] CU occurs more frequently in adults, in the third to fifth decade of life, commonly in women, with a 2:1 ratio.[3] CU is not common in children (prevalence close to 1.8%).[4] In many CU patients symptoms appear more than 3 days a week, for more than 6 weeks.[5,6] Some studies report that 52% of patients with CU achieved remission after 1 year and 88.9% after 5 years regardless of gender, age, geographical area, or association with thyroid disease.[7] CU frequently interferes with sleep time and decreases quality of life.

According to its etiology, CU is classified as inducible chronic urticaria (ICU) and chronic spontaneous urticaria (CSU).[7] ICU is triggered by physical factors such as pressure, sunlight,

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cholinergic stimuli, cold, heat, water, exercise or vibration. It represents about 20% of cases of CU.[1] On the other hand, in the remaining 80% of patients with CU there is no evident eliciting trigger, and it is termed as CSU. The last one has an estimated general prevalence of 0.5–1%.[8,9] CSU is associated with autoimmunity in 30–45% of cases.[6,12]

CSU is associated in 1% of the cases with type 1 diabetes mellitus, rheumatoid arthritis, celiac disease, vitiligo, or hemolytic anemia, and in 4.3–57.4% of cases with autoimmune thyroid disease (ATD), Grave's disease (GD), and autoimmune thyroiditis/Hashimoto's thyroiditis (HT). CSU can begin years before the diagnosis of any of the above mentioned autoimmune diseases (AD).[8,10] Several studies have reported a significant association between autoimmune thyroid disease and chronic urticaria. Leznof et al., reported for the first time that 12.1% of patients with chronic autoimmune urticaria (CAU) had evidence of HT and suggested that both diseases are independent.[11]

Pathophysiology of chronic spontaneous urticaria

The pathophysiological mechanisms of urticaria are diverse. The principal feature is the abnormal degranulation of mast cells, with subsequent release of preformed mediators: histamine, proteases, serotonin, proteoglycans and cytokines, production of platelet activating factor (PAF), vascular endothelial growth factor (VEGF), and arachidonic acid metabolites that trigger vasodilation, increased vascular permeability, cellular recruitment and activation of nerve endings. These mediators induce the typical manifestations of urticaria such as erythema, wheals, angioedema, and pruritus.

Edema, vasodilation, and increased permeability of the postcapillary venules can be observed in the superficial and middle dermis. This includes infiltration of inflammatory cells, mostly CD4 + lymphocytes,[13] in addition to eosinophils, monocytes, basophils and neutrophils, without the presence of necrosis. Also there is basopenia, which is associated with the severity of the disease and normalizes when it subsides.[14]

The profile of cytokines in CSU is constituted by a mixed immune response of Th1/Th2 cells. There may be an increase of IL-4, IL-5 IL-1, IL-6, IL-8, IL-10, IL-33, IL-25, TNF-α, IFN-γ, and thymic stromal lymphopoietin (TSLP), with an increase of serum chemokines (CC and CXC): CXCL8, CXCL9, CXCL10 and CXCL12.[14–17]

Immunological mechanisms (autoreactivity or autoimmunity) have been proposed as major elicitors of mast cell and basophil degranulation in patients with CU.[13,18] Immunoglobulin G (IgG) and IgE autoantibodies, peptides, and complement fragments are able to bind to mast cell membrane receptors, activating them and triggering mediator release.[19]

In 30–50% of the cases, the presence of functional IgG autoantibodies against IgE or the extracellular subunit of the high-affinity IgE receptor (FcεRIα) are present.[6,9] These autoantibodies can also activate the classical complement pathway, with the generation of anaphylatoxins such as fractions C5a and C3a, which bind to its receptor in mast cells and induce their activation and degranulation.[8]

There are additional immunological and non-immunological mechanisms of mast cell activation in CU such as substance P, endorphins, enkephalins, and somatostatin.[14]

Pathophysiology of autoimmune thyroid disease

Autoimmune Thyroid disease (ATD) has a prevalence of 2% in the general population. Hashimoto's thyroiditis (HT) is an autoimmune disease characterized by inflammation of the thyroid gland, follicular destruction, and subsequent hypothyroidism.[19] The basis of treatment for HT is thyroid hormone replacement. Regarding to Graves' Disease (GD), it is characterized by the presence of circulating autoantibodies that bind to and activate the thyroid stimulating hormone receptor (TSHR), with subsequent appearance of goiter and hyperthyroidism. The main treatment for GD consists of antithyroid drugs, radioactive iodine and surgery.[20]

The etiology of ATD is multifactorial, including among them a genetic predisposition, exposure to environmental factors, and certain genetic polymorphisms (HLA-DR3, HLA-DR4, CD40, PTPN22, FOXP3, thyroid-specific genes that encode thyroglobulin and TSHR).[21] Among the non-genetic

factors associated with HT an excess of iodine (the higher the iodine content, the more immunogenic TG) which leads to overstimulation of the intracellular adhesion molecule 1 (ICAM-1) expression in the thyrocytes and infiltration of mononuclear cells has been proposed (Table 1).[19,22] Other non-genetic factors associated with HT are low levels of vitamin D and selenium, drugs (IFN-α, amiodarone), bacteria (*Yersinia enterocolitica, Borrelia burgdorferi, Helicobacter pylori*) and viral infections (hepatitis C virus), as well as stress and environmental pollution (phthalates, bisphenol A, perfluorinated chemicals, polyaromatic hydrocarbons) (Table 1).[2]

Thyroid follicular cells have Toll-like receptors (TLRs), which respond to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These triggers activate innate immunity, CD4 + lymphocytes, the production of proinflammatory cytokines such as IL1-β, γ-IFN, and TNF-α, that later on induce cell damage and apoptosis which are key mechanisms for the development of ATD.[23] In HT, self-reactive CD4 + lymphocytes activate B cells to produce antithyroglobulin (TGAbs) and anti-thyroid peroxidase (TPOAbs) antibodies, while CD8 + lymphocytes induces thyrocyte apoptosis.[24,25] On the other hand, in GD autoantibodies against TSH-R, which activate the synthesis and release of thyroid hormone, are involved.[2]

Association of urticaria and autoimmune thyroid disease

Autoimmunity is characterized by inappropriate activation of the immune system towards its own cells and tissues. This can be directed to a specific organ or cause systemic involvement.[19] The relationship between CSU and autoimmune diseases was reported for the first time by Ravitch in 1907,[16] and in the last decades several authors continue studying this relationship with ATD, being the disease that is more frequently associated with CSU, with association rates ranging from 4.3 to 57.4% in adults, compared with 3.5–8% in children.[26] ATD and CSU have some immunological mechanisms in common, associated with dysregulation of the immune system, an increase in IL-6 serum levels,[27] reduction in the number and function of Treg lymphocytes, and an increase in Th17 lymphocytes.[19]

Autoimmune diseases, including CU, are also associated with atopic diseases;[28] for example, Th2 cell cytokines stimulate eosinophils, which are associated with the pathogenesis of GD.[29] On the other hand, CSU is associated with the presence of IgG or IgE autoantibodies (AAbs) against FcεRIα, antibodies against IgE, and the antithyroid antibodies (ATAbs) TPOAbs and TGAbs[19] (Table 2). In the following paragraphs, the frequency of ATAbs is mentioned in detail.

Chiu et al. found significant associations between CU, atopic, and autoimmune diseases (asthma, atopic dermatitis, allergic rhinitis, systemic lupus erythematosus, ATD, psoriasis, Kawasaki's disease, Sjögren's syndrome, Henoch–Schönlein purpura, and inflammatory bowel disease), and mentioned that these share genetic components and etiological pathways.[28] In addition, Cherrez et al. performed a retrospective study to identify CU etiologies and treatment modalities and observed that among all patients with CSU, 3.6% were associated with ATD.[30]

Several studies mentioned that ATAbs could be positive in 10%–42.5% of patients with CSU. Lunge et al. reported that 10% of patients with CSU had ATAbs, specifically anti-microsomal antibodies (AMA).[31] Wan and Wu, reported that ATAbs were found in 27.3% patients with CSU (16% TGAbs,

1. Diet (excess iodine), vitamin D deficiency and selenium
2. Toxins, environmental pollution, radiation, drugs such as lithium, immunomodulators
3. Demographics (age, parity, female sex)

Table 1. Non-genetic factors associated with Hashimoto's thyroiditis *Weetman AP. The Immunopathogenesis of Chronic Autoimmune Thyroiditis One Century after Hashimoto. Eur Thyroid J. 2013; 1(4):243–250.*

	Sensitivity	Specificity
Immunodot with IgG	55%	100%
ELISA	70%	82.5%

Table 2. Complementary tests in CSU with *anti*-FcεRIα autoantibodies *Ulambayar B, Chen Y-H, Ban G-Y, Lee J-H, Jung C-G, Yang E-M, et al. Detection of circulating IgG autoantibody to FcεRIα in sera from chronic spontaneous urticaria patients. J Microbiol Immunol Infect. 2017 Nov 14. pii: S1684-1182(17) 30238-4. https://doi.org/10.1016/j.jmii.2017.10.003. [Epub ahead of print].*

8.3% TPOAbs, 83.3%) Anti-TSH receptor and mentioned that those were not associated with alterations in thyroid hormone levels or clinical manifestations.[32] Aamir et al. reported in a prospective study elevated titers of TGA and AMA in 42.5% and 57.4% of CU patients, respectively ($p < 0.001$),[33] while Amin et al. in a retrospective longitudinal chart review of patients with CU, found that 15% had a history of thyroid disease, and 28.3% had TAbs (TPOAbs and/or AMA), with no significant differences between males and females.[34] Kim et al. found a prevalence of ATAbs in CU patients of 23.4%, TGAbs and TPOAbs were present in 20.7% and 13.6%, respectively.[35] Nevertheless, Halilovic et al. observed a higher prevalence of TPOAbs of 30% in CU patients.[36]

Patients with CSU and positive autologous serum skin test (ASST) have IgG AAbs versus FcεRIα in 32% of cases.[37] Kessel et al. reported that 15% of patients with CU have ATAbs and 34% have IgE anti-thyroid antibodies; the presence of any of these showed a significant association with the time course of CSU.[38]

Furthermore, Ruggeri et al. performed a bibliographic review on the prevalence of GD and/or antibodies to TSH-R in a small series of patients with CSU.[39] The authors cited the work of Confino-Cohen et al., who found a prevalence of 2.6% in CSU patients, compared to 0.09% in healthy individuals, being the prevalence 4 times lower than that found in HT.[5]

Diagnostic approach

An exhaustive clinical history should be performed, and eliciting factors must be identified. It is important to evaluate the quality of life, disease control, and activity scores with validated tools (e.g. Urticaria activity score [UAS7], Angioedema activity score [AAS], Urticaria control test [UCT], and Chronic urticaria quality of life [CUQoL2]). The presence of signs or symptoms suggesting another disease would suggest to perform complementary studies to discard additional differential diagnoses.[1]

In patients with suspicion of autoimmunity, complementary tests can be performed including investigation of specific autoantibodies, basophil activation test (BAT), ASST, and immunodot with IgG or ELISA for the detection of *anti*-FcεRIα autoantibodies (Table 2).[37]

The ASST is considered a practical method that allows the detection of mast cell-activating serum factors. A positive result is significantly associated with ATD, with a sensitivity of 83.3% and a specificity of 84.09%. In addition, the positive result in 33% of cases is associated with the presence of AMA with a sensitivity of 80% and a specificity of 82% ($p < 0.002$).[31] The ASST correlates positively with expression of the TSH-R gene. This test supports the association between CSU and ATD and can be related to the duration and severity of the disease.[3] Based on the increased frequency of ATD in patients with CSU, it is suggested to investigate thyroid function and ATAbs tests as part of the diagnostic approach (Table 3).[9,40]

Treatment of urticaria and autoimmune thyroid disease

The stepwise scheme for the treatment of CU suggests starting firstly with second-generation non-sedating antihistamines (NSAH) at usual doses and avoiding symptom triggers. A second step consists in increasing the recommended dose of nonsedating antihistamines up to 4 times. If there is no improvement, anti-IgE treatment with omalizumab 300 mg given subcutaneously every 4 weeks, or cyclosporine, are recommended.[1] If clinical improvement is not observed, immunosuppressants can be initiated. Ultimately, biological immunomodulator and intravenous immunoglobulin or plasmapheresis could be

Author	Comments
Kessel et al.[38]	In 203 patients with CSU (without control test) 15% showed ATAbs, 34% had IgE antibodies.
Wan y Wu[32]	60 patients with CSU and 40 healthy controls. ATAbs were present in 27.3% of patients with CSU, (16.6% TGAbs, and 8.3% TPOAbs).
Lunge, et al.[31]	50 patients with CU, positive AMA were reported in 10%. The autologous serum test was reported positive in 24%, of which 33% presented elevated AMA.
Aamir et al.[33]	90 patients with CU, ATAbs positive in 42.5% (TGAbs [42.5%] and AMA [57.4%]).
Amin et al.[34]	221 patients with CU, ATAbs were found in 28% of the patients, more common in women 25.5% vs 11% in males.
Kim et al.[35]	184 patients with CSU, 10.9 had ATAbs (TPOAbs 25 [13.6%] and TGAbs [20.7%])
Ulambayar et al.[37]	125 patients with CSU (64 ASST +, 61 ASST -), AAbs IgG FcεRIα were reported in 24.8% and ATAbs in 24% of patients with CSU, compared to 3.1% in healthy subjects.
Czarnecka-Operacz, et al.[44]	148 with CSU and 148 healthy controls (33 patients with AT13) Significant difference in ATAbs between the groups. TPOAbs (OR 6.69) ($p = 0.0045$) TGAbs (OR 6.01) ($p = 0.013$).
Halilovic et al.[36]	70 patients with CU and 70 controls. It was reported that 11.43% of patients with abnormal thyroid function had presence of TGAbs 23% and TPOAbs 30% compared with healthy subjects 1.42% and 2.86% respectively.

Table 3. Autoantibodies in patients with chronic spontaneous CSU *CSU: Chronic spontaneous urticaria. ATAbs: Antithyroid antibodies. IgE: Immunoglobulin E. TGAbs: Anti-thyroglobulin antibodies. TPOAbs:* Anti-*thyroperoxidase antibodies. CU: Chronic urticaria. AMA: Antimicrosomal antibodies. ASST: Autologous serum skin test. AAbs: Autoantibodies. FcεRI: High-affinity IgE receptor.*

considered as alternative treatments when omalizumab and cyclosporine are not available, are ineffective, or induce intolerable adverse effects.[41,42] It is important to know all treatment options because 40–55% of CSU cases are refractory to maximum antihistamine therapy.[18,37]

In CSU patients with autoimmune diseases, in addition to removing trigger factors when possible the use of antihistamines in high doses, omalizumab, and cyclosporine are effective in 45% of cases.[6] Omalizumab has been associated with clinical improvement of CSU in patients with ATD.[16,42,43] Also, the presence of ATAbs, was associated with poor response to sulfasalazine with an OR 0.01 (0.002–0.4).[34]

Several studies suggest that adequate therapy with antithyroid drugs or levothyroxine in early stages may help to achieve remission of CSU.[44] Kim et al. reported that 2 out of 10 patients with CSU and HT, showed improvement in urticaria symptoms when levothyroxine was administered.[35] Magen et al. reported that patients with CSU and hypothyroidism, showed a decrease of the urticaria activity score (UAS) when levothyroxine was added to the treatment; nevertheless, in euthyroid patients, there was no significant difference after 3–6 months of levothyroxine treatment.[45] Furthermore, Temboury et al. reported a case of a 13-year-old male with CSU and hyperthyroidism, who was treated with levothyroxine and presented improvement in urticaria symptoms;[46] while Milchert et al. reported the case of a 33-year-old male with CSU and ATAbs who presented improvement of the urticaria when treated with L-thyroxine, but the wheals continued despite treatment. Kiyici et al. reported that patients with CSU and positive ATAbs managed with levothyroxine presented clinical improvement of pruritus and

severity of the disease.[17] Moreover, Aversano et al. observed that women with CSU and ATD treated with L-thyroxine showed a reduction of CSU symptoms,[25] while Levy et al. reported that patients with hypothyroidism treated with levothyroxine did not show remission of the illness.[47]

On the other hand, it has been described that 42% of patients with CU have elevated TSH levels in the absence of clinical hypothyroidism. TSH receptors are found in the thyroid gland and in cells of the immune system, and TSH itself can act as a cytokine in thyroid diseases. It is associated with the continuous release of IL-1, IL-2, IL-6, and IL-12 by lymphocytes and dendritic cells.[33]

In the last 15 years, there have been several case reports and studies that evaluate the clinical response of patients with CSU and ATD. The studies differ in methodology, number of cases, patient characteristics, treatment time, and scales of evaluation of symptoms. The clinical results vary from complete improvement to partial reduction of symptoms or the absence of improvement. No double-blind, placebo-controlled studies were found to support the treatment of patients with CSU and HT with or without hypothyroidism using levothyroxine/L-thyroxine (Table 4). The indication of levothyroxine in patients with HT with low TSH and without hypothyroidism depends on the clinical characteristics and physician's expertise.

CONCLUSIONS

The association between CSU and ATD is more common in adult women, ranging from 4.3% to 57.4%. In the approach of both diseases, the ASST

Author	Comments
Kim et al.[35]	184 patients with CU, 23.4% with ATAbs and 14.1% with thyroid dysfunction, were treated with levothyroxine. Only 2/10 patients with HT showed improvement in urticaria. 8 patients presented hyperthyroidism, of which 5 had GD. No patient showed improvement in urticaria after treatment with antithyroid drugs.
Magen et al.[45]	44 cases with CSU and hypothyroidism compared with 44 CSU and euthyroid controls. They were administered L-thyroxine for 53 $\pm$ 19 days. After the treatment, all subjects were euthyroid, the UAS score decreased without showing any relationship with the ASST result. After 3–6 months of treatment, no significant difference was found in the euthyroid controls.
Temboury et al.[46]	A 13-year-old male with recurrent CU and hypothyroidism, increased TGAbs, and TPOAbs (4440 U/ml). 50 µg thyroxine treatment was administered. Patient showed improvement of the CU, until finally becoming asymptomatic.
Kiyici et al.[17]	15 patients with CSU and positive ATAbs, were divided into 2 treatment groups: 1) Levothyroxine and desloratadine 5 mg/day, 2) Desloratadine 5 mg/day. All patients showed significant improvement in pruritus and severity of the hives, but there was no difference in other clinical symptoms or in the levels of antibodies. In group 1 the levels of IFN-γ and TNF-α increased after treatment with levothyroxine compared to basal levels. ($p = 0.05$)
Aversano, et al.[25]	20 women with CSU and AT with positive ATAbs received L-thyroxine until suppression of TSH. In 16 of them there was a decrease in symptoms of urticaria at 12 weeks ($p < 0.0001$), and ATAbs levels ($p = 0.001$).
Levy et al.[47]	187 patients with CSU for more than 7.5 years. Among female patients ($n = 97$) 1 had Hashimoto's thyroiditis, 2 had hypothyroidism. They were given levothyroxine 100 µg/day. None of the 3 showed remission of the disease when starting levothyroxine.

Table 4. Levothyroxine in the treatment of CU (15 years to date)* *CU: chronic urticaria. HT: Hashimoto's thyroiditis. GD: Grave's disease. CSU: chronic spontaneous urticaria. UAS: urticaria activity score. ASST: autologous serum skin test. ATAbs: anti-thyroid autoantibodies, TGAbs: anti-thyroglobulin antibodies. TPOAbs: anti-thyroid peroxidase antibodies. IFN-γ: interferon gamma. TNF-α: tumor necrosis-alpha. AT: autoimmune thyroiditis. TSH: Thyroid stimulating hormone.*

allows initially to detect an underlying autoimmune mechanism or the presence of AAbs, and a probable association between them. ASST may be considered in the first steps of the diagnostic process, and then it would be adequate to perform the investigation of specific antibodies. Although there are several studies that explain the relationship between CU and ATD, there is still a lack of double-blind, placebo-controlled studies that support the use of antithyroid drugs and levothyroxine in patients with CSU and positive ATAbs without alterations in thyroid hormone levels.

Abbreviations

ATAbs: anti-thyroid autoantibodies; AAbs: autoantibodies; AD: autoimmune diseases; AE: angioedema; ASST: autologous serum skin test; ATD: autoimmune thyroid disease; TGAbs: anti-thyroglobulin antibodies; TPOAbs: anti-thyroid peroxidase antibodies; AMA: antithyroid microsomal antibody; BAT: basophil activation test; CU: chronic urticaria; CAU: chronic autoimmune urticaria; CSU: chronic spontaneous urticaria; DAMPs: damage-associated molecular patterns; FcεRIa: high affinity IgE receptor; GD: Graves' disease; ICU: inducible chronic urticaria; IFN-γ: gamma interferon; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IL: Interleukin; NSAH: non-sedating antihistamines; PAF: platelet activating factor; PAMPs: pathogen-associated molecular patterns; TG: thyroglobulin; HT: Hashimoto's thyroiditis/autoimmune thyroiditis; TNF-α: tumor necrosis factor alpha; Treg: regulatory T cells; TSH: thyroid stimulating hormone; TSHR: thyroid stimulating hormone receptor; T4L: free thyroxine; TLR: Toll-like receptors; UAS: urticaria activity score; VEGF: vascular endothelial growth factor

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