

SHORT REVIEW

Chronic idiopathic urticaria and Graves' disease

R.M. Ruggeri¹, S. Imbesi², S. Saitta², A. Campenni³, S. Cannavò¹, F. Trimarchi¹, and S. Gangemi²

¹Unit of Endocrinology; ²School and Unit of Allergy and Clinical Immunology, Department of Clinical and Experimental Medicine;

³Department of Radiological Sciences, Nuclear Medicine Unit University of Messina, Messina, Italy

ABSTRACT. Chronic urticaria is a common condition characterized by recurrent episodes of mast cell-driven wheal and flare-type skin reactions lasting for more than 6 weeks. In about 75% of cases, the underlying causes remain unknown, and the term chronic idiopathic urticaria (CIU) is used to emphasize that wheals develop independently of identified external stimuli. Although CIU affects about 1.0% of the general population, its etiopathogenesis is not yet well understood. It is now widely accepted that in many cases CIU should be regarded as an autoimmune disorder caused by circulating and functionally active IgG autoantibodies specific for the IgE re-

ceptor (FcεRI) present on mast cells and basophils or for IgE itself. The well-known association of CIU with other autoimmune processes/diseases represents further indirect evidence of its autoimmune origin. Autoimmune thyroid diseases, especially autoimmune thyroiditis, represent the most frequently investigated diseases in association with CIU. Here we review this topic with particular regard to the association between Graves' disease and CIU. The possible pathogenetic mechanisms and the clinical implications of such an association are discussed. (J. Endocrinol. Invest. 36: 531-536, 2013)

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INTRODUCTION

Urticaria is a skin affection characterized by itchy wheal, that may vary in size, number, and distribution, and flare type skin reactions (hives) (1). These symptoms and signs are brought about by activated skin mast cells and their subsequent release of histamine and other vasoactive mediators, leading to increased vasodilation, increased vascular permeability and development of edema, erythema, and pruritus (1). Urticaria is a common condition, affecting up to 20% of the population, and it may be associated with angioedema in about 40% of individuals (1-3). Based on etiopathogenesis, urticaria can be classified as reported in Table 1 (1). Based on duration of symptoms, it is subdivided into acute and chronic urticaria. When daily manifestations last for more than 6 weeks, urticaria can be classified as chronic (1, 2). When the cause remains unknown, the term "chronic idiopathic urticaria" (CIU) is used to emphasize that wheals develop spontaneously, i.e. independent of external stimuli (1, 2). This is the case in about 75% of patients (2). CIU is more frequent than commonly thought, affecting 0.5-1% (1, 2) to 3% (3) of the general population. Although all age groups can be affected, it has been reported a peak occurrence in the middle ages, between 20 and 40 years, and a preference for female gender (female:male ratio = 4:1) (1, 4). The duration of the disease is generally 1-5 yr but is likely to be longer in more severe cases, with 20% of patients still having the disease after 20 yr has elapsed, and the clinical course of symptoms

is often unpredictable (3, 4). Moreover, CIU is often resistant to conventional therapies. Thus, CIU has major detrimental effects on quality of life, with sleep deprivation and psychiatric comorbidity being frequent. It also has a large impact on society in terms of direct and indirect health care costs (2, 4). The frequent failure to identify a specific underlying cause contributes greatly to make it difficult to take care of these patients.

ETIOLOGY AND PATHOGENESIS

Although CIU affects about 1.0% of the general population, its etiopathogenesis is not well understood (2, 4). An autoimmune etiology has been suggested in up to one-third of cases, as a result of antibodies against the α -subunit of the high-affinity IgE receptor (Fc ϵ RI α), or against IgE itself (1-3). As early as 1974 Greaves et al. reported that histamine release from blood basophils of unselected patients with CIU was significantly lower than in matched non-urticarial controls, when challenged *in vitro* by a range of concentrations of anti-IgE (5). In 1986 Grattan reported the presence of a serum factor that caused whealing on autologous intradermal injection in some but not all patients with CIU (6). Subsequently, histamine-releasing autoantibodies with functional properties of anti-IgE were found in patients with CIU (7) and in 1993 IgG class antibodies with specificity for the α -chain of the high-affinity IgE receptor (Fc ϵ RI α) were identified (8). Subsequent studies demonstrated that these antibodies are functionally active and able to activate complement, generate C5a, and to cross-link Fc ϵ RI α on mast cells and basophils, leading to the release of granule constituents, such as histamine and other pro-inflammatory and vasoactive mediators (9-16). The IgG subtypes are predominantly IgG1 and IgG3. Also non-functional anti-Fc ϵ RI α autoantibodies have been detected in about 15% of CIU patients; these non-histamine-releasing autoantibodies have been shown to be predominantly IgG2 and

Key-words: Chronic idiopathic urticaria, Graves' disease, thyroid autoimmunity.

Correspondence: R.M. Ruggeri, MD, PhD, Unità di Endocrinologia, Dipartimento di Medicina Clinica e Sperimentale, Padiglione H, 4 piano - Policlinico Universitario "G. Martino", 98125 Messina, Italy.

E-mail: rmruggeri@unime.it

Accepted March 21, 2013.

First published online April 18, 2013.

Table 1 - *Etiopathogenesis of urticaria (1).*

Spontaneous urticaria (with immunological or extrimmunological pathogenesis)	Food Drugs Infections Chronic idiopathic urticaria
Physical urticaria	Cold contact urticaria Delayed pressure urticaria Localized heat urticaria ^a Solar urticaria Dermographic urticaria/Factitia urticaria, Vibratory urticaria/angioedema ^a
Other types	Contact urticaria Exercise induced urticaria Acquagenic urticaria Cholinergic urticaria Vasculitis urticaria
Diseases/Syndromes related to urticaria	Non-histaminergic angioedema (e.g. Hereditary angioedema) ^a C3b-inactivator deficiency ^a Carboxypeptidase N deficiency ^a Urticaria pigmentosa (mastocytosis) Familial cold urticaria ^a Muckle-Wells syndrome (with deafness and amyloidosis) ^a Erythropoietic protoporphyria with solar urticaria ^a Schnitzler's syndrome (with monoclonal gammopathy, recurrent fever, arthritis) Gleich's syndrome (episodic angioedema with eosinophilia and IgM gammopathy) Well's syndrome (Eosinophilic cellulitis)

^aHereditary pathogenesis.

IgG4 subclass, which do not activate complement (16). Functional anti-Fc ϵ RI α antibodies have been found in about 25% of patients, the frequency ranging from 25% to 45% of the total patients with CIU (11, 12, 16), and their presence has been related to more severe disease (16). A further 5% of patients proved to have functional anti-IgE autoantibodies (10). Other circulating factors, including the mast cell-specific non-antibody histamine-releasing factor, have been demonstrated in another 9% of patients (16). But what about the other 40% of CIU patients? Indirect evidence suggests that many of the remainder may also be autoimmune in origin (2, 3).

CHRONIC IDIOPATHIC URTICARIA AND AUTOIMMUNE DISEASES

The well-known association of CIU with other autoimmune processes/diseases represents further indirect evidence of its autoimmune origin (2, 4, 7, 17). Autoimmune thyroid disease is the most frequently investigated disease in association with CIU (18). As early as 1983 Leznoff et al. reported that 12% of patient with CIU had increased serum titers of thyroid microsomal antibodies as compared to 5.6% of healthy controls (19). A few years later, Leznoff and Sussman (20) proposed a relation between CIU/angioedema "syndrome" and autoimmune thyroid disease, with thyroid autoantibodies identified in 15% of patients (20). Subsequently, several studies approached this issue, but many consisted of small, not well-controlled series (18). Overall, CIU patients have been reported to frequently suffer from autoimmune thyroiditis and increased serum levels of anti-thyroid antibodies were reported with frequency ranging from 6.5% to 57% among CIU patients (18, 21-24). However, most studies

have suggested that these autoantibodies do not play a direct causative role in CIU, but rather represent a parallel, auto-immune event (18, 25, 26). Recently, Altrichter et al. showed that a sizeable subgroup of CIU patients exhibits IgE antibodies against thyroid peroxidase (TPO) (27). Such IgE autoantibodies were first demonstrated by Bar Sela et al. in the serum of a female patient who suffered from CIU and Hashimoto's thyroiditis (HT), suggesting a pathogenetic role in urticarial symptoms (28). Subsequent studies failed to reproduce these findings in large series of patients with CIU and thyroid autoimmunity, and the detection of IgE specific for TPO was considered an occasional finding, not relevant for the activation of mast cells and basophils (29, 30). In the recent study by Altrichter et al. (27) elevated serum levels of IgE-anti-TPO were detected in about half of CIU patients (54.2%), by using a site-directed human IgE capture enzyme-linked immunosorbent assay. Anti-TPO-IgE-positive patients exhibited significantly higher levels of anti-TPO-IgG, as well as decreased C4 complement levels. These anti-TPO-IgE autoantibodies, when bound on the surface of mast cells, could cause 'autoallergic' mast cell activation and degranulation, thus playing an active role in the pathogenesis of CIU, at least in a subgroup of patients (27). Moreover, autoallergen mimicry cannot be excluded, as the extracellular domain of TPO has a similarity of around 45% with myeloperoxidases from eosinophils (31). Also, it has been hypothesized that anti-TPO-IgE could cross-react with peroxidases of common pathogens or vegetables, and that the exposure to environmental allergens or infectious agents could trigger urticaria (18, 27, 29). Again, it has been reported that antigen mimicry between aeroallergens and thyroid antigens may be responsible for the alteration in the levels of

thyroid autoantibodies. These effects of allergic sensitization did not depend on the presence of allergic symptoms (32). Finally, resolution of urticaria after L-T₄ treatment has been reported by some authors (18) and an overall correlation has been found between urticaria improvement and decrease of serum thyroid autoantibodies (33). It has been hypothesized that TSH would stimulate both the production of antithyroid antibodies and the synthesis of proinflammatory cytokines by lymphocytes and monocytes, so as to maintain an inflammatory status, leading to urticarial symptoms. L-T₄ therapy could reduce cytokines production, as well as TPO/thyroglobulin antibodies (TgAb)-mediated complement activation, by decreasing serum TSH and thus serum thyroid autoantibodies (18, 33). However, a common pathogenesis of the CIU and autoimmune thyroid disease, although so suspected, cannot be proved. The association between the two diseases might be due to a shared susceptibility to autoimmune processes. This hypothesis is supported by the additional finding that CIU may also be associated with autoimmune conditions other than thyroid diseases. Once again, most of these reports include small series of patients or case reports. For example, celiac disease was reported in children and adolescents with CIU, and most cases showed improvement or resolution of the urticaria with a gluten-free diet (34). Asero et al. reported Raynaud phenomenon with anticentromere antibodies in five (2%) out of 257 CIU patients, and one of them had mixed connective tissue disease, with typical clinical and serologic features (35). Ryahl et al. investigated serologic markers of autoimmunity in a small cohort of 25 patients with CIU, compared to 75 control subjects being treated for other allergic diseases. They demonstrated that TPO-Ab and rheumatoid factor were more commonly found in CIU patients (20% and 16%, respectively) than in controls (0%), but other markers of autoimmunity were not found (36). More recently, a large population study demonstrated that about 15% of CIU

patients (1872 out of 12,778 patients) had one or more autoimmune diseases associated (17). Beside autoimmune thyroid diseases, female patients with CIU had a significantly higher incidence of rheumatoid arthritis, Sjögren syndrome, systemic *lupus erythematosus*, celiac disease, and Type 1 diabetes mellitus, mostly diagnosed during the 10 yr after the diagnosis of CIU (17). Positive rheumatoid factor, and antinuclear antibodies were all significantly more prevalent in CIU patients than in a control group comprised of 10,714 patients (17).

CHRONIC IDIOPATHIC URTICARIA AND GRAVES' DISEASE

Early reports of urticarial manifestations in the course of hyperthyroidism date back to the 1950s and predate the first report in 1983 of an association between chronic urticaria and autoimmune thyroiditis (37-40). In subsequent years several reports of such an association between CIU and Graves' disease (GD) have followed (41-53). Beside articles describing just one or a few patients (41-43, 46, 47, 49, 51, 52), other articles have evaluated the prevalence of GD and/or positivity of TSH-receptor antibodies (TRAb) in small series of patients affected by CIU, as summarized in Table 2. For instance, in their assessment of 154 patients with CIU, Small and Lerman (40) found 6 patients with autoimmune hyperthyroidism (3.9%), 4 of whom also had *polycythemia vera*. Collet et al. (44) reported that 8 among 45 CIU patients (18%) had an autoimmune thyroid disease, and of these one was suffering from GD. Gaig et al. (45) measured Ab-Tg and Ab-TPO levels in the serum of 170 consecutive patients with CIU and found the 45 of them (14.7%, all but three women) were positive for at least one anti-thyroid antibody. Only two of the patients with positive anti-thyroid antibodies (8% or 1.2% of the whole group of patients with CIU) had GD. In a Turkish study (51) 41 of 140 (29%) patients with CIU had positive antithyroid antibodies. Again,

Table 2 - Summary of the data available in the literature about the association between chronic idiopathic urticaria (CIU) and Graves' disease (GD).

Authors, year	Country	Study type	No. of patients with CIU	No. of CIU patients with GD (%)	No. of control subjects	No. of control subjects with GD (%)	Reference no.
Small & Lerman, 1981	Canada	Prospective	154	6 (4%)	No control group	-	39
Cailleba et al., 1984	France	Case report	-	1	No control group	-	40
Altus et al., 1993	USA	Case report	(2)	1	No control group	-	41
Henderson & Highet, 1995	UK	Case report	-	1	No control group	-	42
Collet et al., 1995	France	Prospective	45	1 (2%)	No control group	-	43
Gaig et al., 2000	Spain	Prospective (no placebo-controlled)	170	2 (1%)	No control group	-	44
Irani et al., 2001	Italy	Case report	-	1	No control group	-	45
Verneuil et al., 2004	France	Prospective	45	-	30	-	47
Caproni et al., 2004	Italy	Prospective	68	5 (7.35%) ^a	No control group	-	49
Asero et al., 2005	Italy	Case report	-	1	No control group	-	48
Cebeci et al., 2006	Turkey	Prospective	140	2 (1.4%)	181	1 (0.5%)	49
Monge et al., 2007	USA	Case report	-	2	No control group	-	50
Bansal & Hayman, 2009	UK	Case report	-	2	No control group	-	51
Confino-Cohen et al., 2012	Israel	Retrospective	12,778	336 (2.6%)	10,714	10 (0.09%) ^b	17

^a5 out of 68 CIU patients had positivity of anti-TSH receptor antibodies. ^b*p*<0.005 as compared to the 2.6% prevalence of GD in CIU patients.

only a minority of such patients had GD (2 of the 140 CIU patients or 1.4%). Overall these studies showed that CIU was more frequently associated with HT than with GD. These results were in line with a study by Verneuil and co-workers (48) that evaluated the prevalence of TRAb, as well as the Tg-Ab and TPO-Ab, in patients with CIU (48). The Authors compared the frequency of anti-thyroid antibodies in 30 healthy individuals and 45 patients with CIU, demonstrating a statistical association between TPO-Ab and Tg-Ab, and CIU; the frequency of these antibodies in CIU patients was 26.7% compared to 3.3% in healthy subjects ($p < 0.01$) (48). Such an association was not found with TRAb, and all the patients with thyroid autoantibodies had thyroid hormone concentrations within the normal limits. In the same year, an Italian survey demonstrated TRAb positivity in a non-negligible proportion of patients with CIU (5 out of 68 patients, or 7%, compared to 9 patients, or 13%, with TPO-Ab and/o Tg-Ab positivity) (49). This study, however, was lacking a control group (49). On this basis, in a review of 2011 Bagnasco et al. concluded that "... there is much less support for an association between GD and CIU compared to the data supporting an association between CIU and serological evidence for autoimmune thyroiditis" (18). In a more recent study by Confino-Cohen et al., the prevalence of autoimmune thyroid disease was evaluated in a large unselected population of 12,778 patients given a diagnosis of CIU, compared to a control group comprised of 10,714 patients (17). The Authors found that anti-thyroid antibodies (TPO-Ab and Tg-Ab) were found significantly more in CIU patients than in control subjects, and about 10% of CIU patients had hypothyroidism, compared with 0.6% in the control group ($p < 0.0005$). Hyperthyroidism was less common in both group, but yet it was significantly more prevalent in the CIU group than in the control group (2.6% and 0.09%, respectively; $p < 0.0005$). Moreover, odd risk (OR) for having hyperthyroidism was 34.98 times greater for female patients with CIU compared with the OR in the control group, and 19.73 when comparing male patients ($p < 0.0005$), and these values were even greater than the odds of having hypothyroidism (17). The 2.6% prevalence of hyperthyroidism reported in this study on a large population, as well as the 1.2% to 4% prevalence reported in previous studies (40, 44, 45, 51), although lower than that of hypothyroidism, is still higher than the 0.5-1% reported in the general population (54). Thus, such an association is real, but probably underestimated. Obviously, its epidemiological impact is less than that of the association between CIU and HT. This is mainly due to the fact that GD is far less common than autoimmune thyroiditis or the sole positivity of thyroid autoantibodies, estimated at around 2-5% and 16-20%, respectively, in the general population (55). Moreover, a confounding factor in evaluating the association between CIU and GD is that many of the patients with GD may be taking anti-thyroid drugs (methimazole, carbimazole, or propylthiouracil) that, in themselves, may cause itching and, less frequently, urticaria.

Regardless of the prevalence, the association between GD and CIU is of interest from a patho-physiological point of view. As first noted by Irani et al. (46), both GD and CIU are

characterized by the presence of anti-receptor antibodies (TRAb and $Fc\epsilon RI_{\alpha}$, respectively), that act as agonists and are functionally active, and in this they differ from most autoimmune disease, in which autoantibodies or autoreactive T cells promote the destruction and affect the function of the target tissue. Although there is no homology between the protein sequences of TSHR and $Fc\epsilon RI_{\alpha}$, the Authors hypothesized that the 3-dimensional structures could give rise to a shared conformational B cell epitope (46). However, a causal relationship with TRAb has not been established (48, 50). Moreover, it is well known that a common link between GD and allergic immune response exists. This is demonstrated by the fact that elevation of serum levels of IgE has been reported in one-third of patients affected by GD (but not in HT patients), and serum levels of TRAb are significantly related with total IgE (56-60). GD patients with elevated IgE showed a low rate of remission after treatment with anti-thyroid drugs and a high recurrence rate even after remission (57, 58). Also the prevalence of seasonal allergic rhinitis was found to be significantly higher in GD patients (42.9%, $p < 0.05$), but not in HT patients (26.1%), compared to healthy controls (32.6%) (60). This may be due to a close cross-talk between the allergic and immune reactions in GD.

On the clinical ground, improvement of CIU after therapeutic correction of hyperthyroidism has been reported by some authors (43, 45, 53). As early as 1995, Henderson and Highet reported the case of a patient with CIU which was closely associated with elevated levels of free T_4 (FT_4). The urticaria responded poorly to antihistamines but resolved consistently when FT_4 levels normalized (43). Gaig et al (45) reported 2 patients with GD who improved rapidly after therapeutic normalization of their thyroid function. More recently, Bansal and Hayman (53) described two patients with CIU poorly responsive to antihistamines and corticosteroids, who developed symptomatic hyperthyroidism within 6 months of the onset of their urticaria. In both patients urticarial symptoms quickly ameliorated as carbimazole treatment was started and the patients became euthyroid (53). Unfortunately, these are anecdotal reports regarding only one or a few number of patients, as well as are studies concerning L- T_4 therapy in HT. In the absence of well-conducted placebo-controlled studies, it is difficult to ascertain whether anti-thyroid drugs are really effective or whether there is a natural improvement of the CIU. Certainly, the rapid amelioration of CIU observed may be due to a reduction in sweating and heat intolerance experienced by the patient when thyroid hyperfunction is reduced. Moreover, hyperthyroidism *per se* causes itching. However, anti-thyroid drugs decrease the synthesis (and serum levels) not only of thyroid hormones, but also of thyroid autoantibodies probably due to immunosuppressive effects, that contributes to remission of GD (61). In the same manner, they may influence the clinical course of CIU of autoimmune origin.

In conclusion, coexisting GD has been reported in CIU patients, with an estimated prevalence ranging between 1.2 to 4%. Such a prevalence, although lower than that of autoimmune thyroiditis, is still higher than the 0.5-1% reported in the general population, indicating that the association between the two diseases is not merely casual.

Indeed, this association is well recognized in the context of autoimmune polyendocrine syndromes (APS), namely the type 3 APS (62, 63). Screening for thyroid autoimmunity is useful in CIU patients and can help clinicians to identify a potential or subclinical autoimmune disease. Data concerning the influence of hyperthyroidism cure on CIU outcome are scanty and not conclusive, but an overall improvement of urticaria as thyroid function returns to normal is suggested.

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