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Original Article

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Autoimmune Diseases Are Linked to Type IIb Autoimmune Chronic Spontaneous Urticaria

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ABSTRACT

Purpose: Patients with chronic spontaneous urticaria (CSU) have an increased risk for comorbid autoimmune diseases. In this retrospective multicenter study of CSU patients, we evaluated clinical and laboratory features of CSU associated with a higher risk of comorbid autoimmune diseases.
Methods: We analyzed records of CSU patients (n = 1,199) for a history or presence of autoimmune diseases. Patients were diagnosed with type IIb autoimmune CSU (aiCSU) if all 3 tests were positive: autologous serum skin test (ASST), basophil histamine release assay (BHRA) and/or basophil activation test (BAT), and IgG autoantibodies against FcεRIα/IgE detected by immunoassay.
Results: Twenty-eight percent of CSU patients had at least 1 autoimmune disease. The most prevalent autoimmune diseases were Hashimoto's thyroiditis (HT) (≥ 21%) and vitiligo (2%). Two percent of CSU patients had ≥ 2 autoimmune diseases, most frequently HT

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plus vitiligo. Comorbid autoimmune diseases, in patients with CSU, were associated with female sex, a family history of autoimmune diseases, and higher rates of hypothyroidism and hyperthyroidism ($P < 0.001$). Presence of autoimmune diseases was linked to aiCSU ($P = 0.02$). The risks of having autoimmune diseases were 1.7, 2.9 and 3.3 times higher for CSU patients with a positive ASST, BHRA and BAT, respectively. In CSU patients, markers for autoimmune diseases, antinuclear antibodies and/or IgG anti-thyroid antibodies were associated with non-response to omalizumab treatment ($P = 0.013$).

Conclusions: In CSU, autoimmune diseases are common and linked to type IIb autoimmune CSU. Our results suggest that physicians assess and monitor all adult patients with CSU for signs and symptoms of common autoimmune diseases, especially HT and vitiligo.

Keywords: Chronic urticaria; autoimmune diseases; autoimmune thyroiditis; autoantibodies; autoimmunity; omalizumab; vitiligo; immunoassay

INTRODUCTION

Chronic spontaneous urticaria (CSU) is defined as the spontaneous occurrence of wheals, angioedema or both for > 6 weeks due to known or unknown causes.[1] While exact pathomechanisms underlying CSU are, as of yet, not completely unraveled, there is strong evidence to support a link to autoimmunity.[2,3]

Recently, 2 endotypes of CSU have been proposed: type I autoimmune CSU mediated by IgE autoantibodies (also known as autoallergic CSU) and type IIb autoimmune CSU (aiCSU),[4-7] in which IgG autoantibodies, and probably IgM and IgA are responsible for direct activation of mast cells by binding to high-affinity IgE receptors.[3,8] Positive autologous serum skin test (ASST), basophil histamine release assay (BHRA) and immunoassay for specific IgG autoantibodies against FcεRIα/IgE are the current gold standard for the diagnosis of aiCSU.[9] At least 8% of CSU patients have aiCSU and they are more severely affected with markedly lower total IgE levels,[4] and higher rates of eosinopenia and basopenia.[10]

On the other hand, CSU patients are known to often exhibit comorbid autoimmune disorders,[4,11-14] mostly Hashimoto's thyroiditis (HT), vitiligo and rheumatoid arthritis.[11,12] Also, CSU has been described to occur in patients with common autoimmune diseases such as autoimmune thyroid disease (AITD) and relatively rare autoimmune disorders, *e.g.* autoimmune encephalitis.[11,15-17] CSU is thought to occur more frequently in patients with AITD, systemic lupus erythematosus (SLE), rheumatoid arthritis or celiac disease.[11,17]

Three reasons underline the importance of research on the role and relevance of autoimmune diseases in CSU. First, the presence of autoimmune diseases in patients with CSU may predict the duration, activity and course of CSU and the response to treatment. Secondly, various features of CSU may be associated with a higher risk of having comorbid autoimmune diseases. Knowledge of these features can help facilitate early diagnosis of comorbid autoimmune diseases in patients with CSU. Thirdly, therapeutic interventions in patients with CSU and concomitant autoimmune diseases need to be aligned to assure maximum efficacy as well as minimum drug interactions and adverse effects. For example, CSU treatment, *e.g.* omalizumab or cyclosporine, may also be effective in some other autoimmune diseases, *e.g.* SLE,[18] bullous pemphigoid,[19] eosinophilic granulomatosis with polyangiitis[20] and autoimmune polyglandular syndromes.[21]

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Thus, the link between CSU and autoimmunity has been known for many years, although the specific distribution of autoimmune diseases in different CSU phenotypes and endotypes is less characterized. In this multicenter retrospective study with more than 1,000 CSU patients, we evaluated clinical and laboratory factors associated with a higher risk of having autoimmune diseases and we characterized this subpopulation of patients.

MATERIALS AND METHODS

Patients

We analyzed data from 1,199 CSU patients from the urticaria specialty clinics of Charite-Universitätsmedizin Berlin, Germany (n = 791), I.M. Sechenov First Moscow State Medical University, Russia (n = 249) and 10 further collaborating urticaria centers (n = 159, the PURIST study, some data have been published before[4]). Patient data were analyzed retrospectively. The study followed Good Clinical Practice guidelines and the Declaration of Helsinki, ethics approval was obtained by each of the cooperating centers as required, and all patients provided signed informed consent. CSU was defined as recurrent whealing, angioedema, or both for > 6 weeks due to known or unknown causes and without definite triggers. Patients with chronic inducible urticaria alone and patients with urticarial vasculitis were excluded.

Autoimmune diseases

We analyzed the patients' records for a history or presence of autoimmune diseases including vitiligo, rheumatoid arthritis, celiac disease, type I diabetes mellitus, SLE, autoimmune gastritis/pernicious anemia, ankylosing spondylitis, alopecia areata, myasthenia gravis, antiphospholipid syndrome, scleroderma, idiopathic thrombocytopenic purpura, dermatomyositis, primary biliary cirrhosis and autoimmune hepatitis. CSU patients with several other conditions such as psoriasis, endometriosis, fibromyalgia, sensorineural hearing loss and thrombocytopenia, in which an autoimmune nature of the disease has been discussed, but not ultimately confirmed, were excluded from the analyses unless other autoimmune diseases were present. AITD was assessed if diagnosed by a physician and/or elevated levels of IgG anti-TPO with euthyroidism, hypothyroidism (HT) or hyperthyroidism (Graves' disease) were present. A few patients with CSU and hypothyroidism might have normal thyroid hormones levels because of the levothyroxine treatment.

Clinical and laboratory parameters

Blood was drawn and analyzed for routine patient care. From the patients' record, we extracted data on age, sex, duration of CSU, presence of concomitant angioedema, family history of autoimmune diseases, disease activity and ASST results, complete blood count, antinuclear antibodies (ANA), serum total IgE and IgG anti-TPO levels, when available.

We analyzed rates of autoimmune diseases in 4 age groups of CSU patients (< 20, 20–29, 30–39, > 39 years) based on the previously reported data on the most common mean age-of-onset of autoimmune diseases of 20–29 and 40–50 years.[22] Disease activity was determined using the urticaria activity score (UAS), which was calculated as the sum of the itch (no = 0, mild = 1, moderate = 2, intense = 3) and the wheal score (no wheals = 0, < 20 wheals/24 hr = 1, 20–50 wheals/24 hr = 2, > 50 wheals/24 hr = 3) for 7 consecutive days (UAS7, minimum = 0, maximum = 42). CSU patients were divided into 3 groups according to CSU activity: low

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disease activity = 0–15 (urticaria-free, well-controlled CSU or mild CSU); moderate disease activity = 16–27 (moderate CSU); and high disease activity = 28–42 (severe CSU).[23]

Type IIb autoimmune CSU

The aiCSU is defined according to an agreed set of 3 diagnostic criteria: (a) positive *in vivo* autoreactivity (positive ASST); (b) positive *in vitro* BHRA and/or basophil activation test (BAT) as evidence of functional serum histamine-releasing autoantibodies in patients' sera that are directed against IgE or high-affinity IgE receptors; and (c) a positive immunoassay for detection of IgG autoantibodies against FcεRIα and/or anti-IgE. The ASST is a screening test for aiCSU that evaluates the presence of histamine-releasing serum factors of any type, including IgG autoantibodies against FcεRIα or IgE. The ASST is regarded as positive when the serum wheal is ≥ 1.5 mm as compared to the negative control (saline).[24] In CSU patients from the PURIST study (n = 159), all three aiCSU-defining tests were performed as previously described.[4]

Most analyses were performed in all centers, except BHRA/BAT, IgG anti-FcεRIα/IgE (data from the PURIST study) and UAS7 (data from the urticaria clinic of Berlin and the PURIST study). UAS7 was usually calculated seven days before the blood sampling and ASST.

Response to treatment

The association between the presence of markers of autoimmune diseases, namely ANA and IgG anti-TPO, and omalizumab 300 mg treatment was retrospectively analyzed in 45 CSU patients from the Berlin cohort. Of 45 patients, seven, 18, and 20 were non-responders (a reduction in UAS7 of less than 30%), partial responders (a reduction in UAS7 of 30% to 89%) and complete responders (a reduction of 90% or more from baseline in UAS7) to omalizumab, respectively. Pre-omalizumab treatment measurements of ANA and IgG anti-TPO were used for this analysis.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Science (IBM SPSS version 25.0; IBM Corp, New York, NY, USA). Figures were made using GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA). Due to the methodology, there were missing data for some variables, and some analyses were performed in subgroups. Demographic characteristics of CSU patients were reported using descriptive statistics. Because data were not distributed normally, non-parametric tests were used. Groups were compared using the Mann-Whitney *U* test, the chi-square test of homogeneity and Fisher's exact test (if data violated the sample size adequacy assumption). *P* values < 0.05 were considered significant. *Post hoc* analysis involved pairwise comparisons using the *z* test of 2 proportions or multiple Fisher's exact tests with Bonferroni correction (statistical significance was set at $P < 0.02$).

RESULTS

Autoimmune diseases, mostly HT, are common in CSU patients

Of 1,199 CSU patients, 28% (n = 333) had one or more comorbid autoimmune disease (**Table 1**). The most prevalent disease was AITD (25%, mostly HT, ≥ 21%). Other autoimmune comorbidities were seen in 3% of cases, mainly vitiligo (2%) and rheumatoid arthritis (1%). Of the 333 CSU patients with a comorbid autoimmune disease, 91% had one, most often AITD, 8% had 2, and less than 1% had 3 (**Table 2**). About 1% of all CSU patients had HT and vitiligo, the most frequent combination of 2 comorbid autoimmune diseases (**Table 2**).

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Table 1. The prevalence of autoimmune diseases in CSU patients

Disease	Prevalence of AID in the general population,%*	Prevalence of AID in CSU						
		% (No./total)	Years of age, % of total				Sex, %	
			< 20	20–29	30–39	> 39	F	M
Any AID	3.9–10.6	27.8 (333/1,199)†	0.5	4.7	4.9	17.5	32.7	14.2
Autoimmune thyroid disease	2.6–4.8	25.4 (305/1,199)‡	0.5	4.2	4.6	15.9	31.2	11.7
Vitiligo	0.02–0.2	2.3 (20/885)	0.1	0.5	0.3	1.2	1.8	3.2
Rheumatoid arthritis	0.1–0.5	1.0 (9/874)	0.0	0.0	0.1	0.9	1.0	1.1
Autoimmune gastritis	0.03–0.1	0.9 (7/755)§	0.0	0.0	0.4	0.5	1.2	0.4
Diabetes mellitus type I	0.1–0.6	0.5 (4/752)	0.0	0.1	0.3	0.1	0.4	0.8
Ankylosing spondylitis	0.07–0.1	0.5 (4/869)	0.0	0.0	0.0	0.5	0.5	0.4
Celiac disease	0.2–0.3	0.3 (2/750)	0.0	0.3	0.0	0.0	0.4	0.0
Primary biliary cirrhosis	0.01–0.03	0.2 (2/867)	0.0	0.0	0.1	0.1	0.3	0.0
Autoimmune hepatitis	0.01–0.02	0.2 (2/920)	0.0	0.1	0.1	0.0	0.4	0.0
Alopecia areata	0.2	0.1 (1/866)	0.0	0.1	0.0	0.0	0.0	0.4
Myasthenia gravis	0.008–0.04	0.1 (1/920)	0.0	0.0	0.0	0.1	0.0	0.5
Antiphospholipid syndrome	0.03–0.04	0.1 (1/749)	0.0	0.1	0.0	0.0	0.2	0.0
Scleroderma	0.009–0.08	0.1 (1/749)	0.0	0.0	0.0	0.1	0.2	0.0
ITP	0.04–0.06	0.1 (1/920)	0.0	0.0	0.0	0.1	0.2	0.0
SLE	0.03–0.15	0.1 (1/866)	0.0	0.0	0.1	0.0	0.2	0.0
Dermatomyositis	0.008–0.019	0 (0/865)	0.0	0.0	0.0	0.0	0.0	0.0

CSU, chronic spontaneous urticaria; AID, autoimmune diseases; F: female; M: male; ITP, idiopathic thrombocytopenic purpura; SLE, systemic lupus erythematosus.
*References[25,53]; †Some patients had more than one autoimmune disease; ‡HT in 20.7% (248/1,199) of patients, Graves' disease in 1.2% (15/1,199) of patients, and diagnosis of autoimmune thyroid disease is not specified in 3.5% (42/1,199) of patients; §Pernicious anemia in 0.4% (3/751) of patients.

Table 2. The number and combination of autoimmune diseases in CSU patients

AID, No.	Prevalence in all CSU patients with AID, %*	Prevalence in all CSU patients, %†
Number of AID in CSU		
One, 304	91.3	25.4
Two, 28	8.4	2.3
Three, 1	0.3	0.1
Four or more, 0	0	0
Combination of CSU with two or more autoimmune diseases		
AITD + vitiligo, 12	3.6	1.0
AITD + autoimmune gastritis,‡ 6	1.8	0.5
AITD + rheumatoid arthritis, 3	0.9	0.2
AITD + ankylosing spondylitis, 2	0.6	0.2
AITD + vitiligo + myasthenia gravis, 1	0.3	0.1
AITD + diabetes mellitus type I, 1	0.3	0.1
AITD + celiac disease, 1	0.3	0.1
AITD + antiphospholipid syndrome, 1	0.3	0.1
Vitiligo + alopecia areata, 1	0.3	0.1
Primary biliary cirrhosis + autoimmune gastritis, 1	0.3	0.1

CSU, chronic spontaneous urticaria; AITD, autoimmune thyroid disease; AID, autoimmune diseases.
*Total = 333; †total = 1,199; ‡Two patients had pernicious anemia.

CSU patients who were 40 years or older had autoimmune comorbidities, especially AITD, RA and vitiligo, more often than younger patients (**Table 1**).

Autoimmune comorbidities, in patients with CSU, are associated with being female and having a family history of autoimmunity

Autoimmune comorbidities were reported more frequently in female CSU patients (risk ratio [RR] = 2.3, $P < 0.001$) and patients with a family history of autoimmune diseases (RR = 2.0, $P < 0.001$; **Table 3**, **Supplementary Table S1**). Patients with angioedema also had higher rates of comorbid autoimmune diseases (RR = 1.2, $P = 0.05$, **Table 3**).

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Table 3. Associations between the presence of autoimmune diseases and clinical/laboratory parameters in patients with chronic spontaneous urticaria

Parameter	AID is present, % (No./total)	AID is absent, % (No./total)	*P* value	RR (95% CI)
Gender			< 0.001	2.31 (1.73–3.08)
F	32.7 (288/881)	67.3 (593/881)		
M	14.2 (45/318)	85.8 (273/318)		
Presence of angioedema			0.05	1.21 (1.00–1.46)
+	30.2 (180/596)	69.8 (416/596)		
–	24.9 (137/550)	75.1 (413/550)		
Family history of AID			0.001	1.99 (1.44–2.75)
+	63.6 (21/33)	36.4 (12/33)		
–	31.9 (72/226)	68.1 (154/226)		
Disease activity (UAS7)			0.135	-
Low	22.2 (94/424)	77.8 (330/424)		
Moderate	27.1 (88/325)	72.9 (237/325)		
High	29.1 (48/165)	70.9 (117/165)		
TSH			< 0.001*	-
↑	67.6 (23/34)	32.4 (11/34)		
Normal	23.7 (143/604)	76.3 (461/604)		
↓	53.6 (15/28)	46.4 (13/28)		
Total IgE, kU/L‡			< 0.001	1.9 (1.57–2.30)
< 50	40.1 (151/377)	59.9 (226/377)		
≥ 50	21.0 (146/696)	79.0 (550/696)		
Basopenia§			< 0.001	2.2 (1.79–2.69)
+	49.3 (73/148)	50.7 (75/148)		
–	22.4 (198/883)	77.6 (685/883)		
Eosinopenia§			< 0.001	1.76 (1.35–2.30)
+	40.6 (41/101)	59.4 (60/101)		
–	23.0 (203/884)	77.0 (681/884)		
IgG-anti-FcεRIα/IgE			0.429	1.08 (0.88–1.34)
+	27.5 (25/91)	72,5 (66/91)		
–	33.3 (22/66)	66.7 (44/66)		
BAT			< 0.001	3.32 (2.18–5.06)
+	67.6 (23/34)	32.4 (11/34)		
–	20.3 (25/123)	79.7 (98/123)		
BHRA			< 0.001	2.9 (1.92–4.37)
+	70.0 (14/20)	30.0 (6/20)		
–	24.1 (34/141)	75.9 (107/141)		
ASST			< 0.001	1.68 (1.39–2.03)
+	37.2 (140/376)	62.8 (236/376)		
–	22.1 (166/751)	77.9 (585/751)		
Type IIb autoimmune CSU			0.02†	-
+	60.0 (9/15)	40.0 (6/15)		
+/–	27.8 (35/126)	72.2 (91/126)		
–	16.7 (3/18)	83.3 (15/18)		

AID, autoimmune disease; RR, risk ratio; CI, confidence interval; F, female; M, male; TSH, thyroid-stimulating hormone; +, positive/present; –, negative/absent; ↑, increased; ↓, decreased; BAT, basophil activation test; BHRA, basophil histamine release assay; ASST, autologous serum skin test; CSU, chronic spontaneous urticaria.
*Comparison between groups: The number of CSU patients with high normal/high or low TSH levels vs. patients with normal TSH levels: $P < 0.001$; †Comparison between groups: Type IIb autoimmune CSU (+) vs. partly type IIb (+/–) CSU: $P = 0.01$, type IIb autoimmune CSU vs. non type IIb autoimmune CSU (–): $P = 0.01$, partly type IIb autoimmune CSU vs. non type IIb autoimmune CSU: $P = 0.402$; ‡In previous studies various cut-off values less than 50 kU/L were used; §Basopenia was defined as blood basophil numbers less than 0.01×10^9/L. For eosinopenia/low blood eosinophil counts, we used a cutoff of less than 0.05×10^9/L as described before.[37]

The presence of autoimmune diseases in CSU patients tended to be associated with higher disease activity (**Table 3**, **Fig. 1A and B**).

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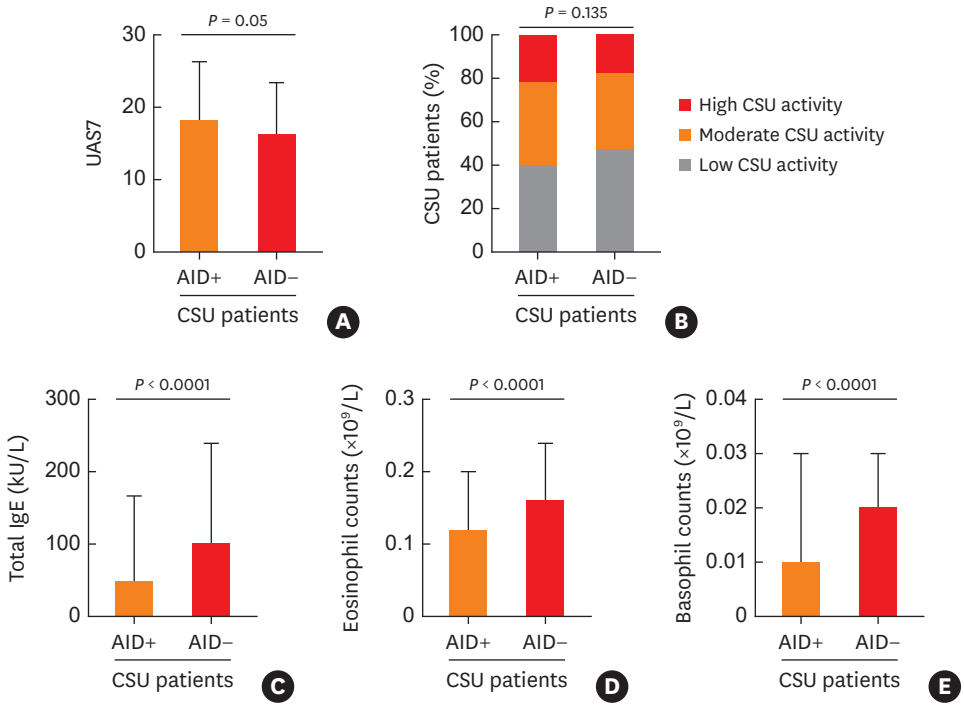

Fig. 1. The presence of autoimmune diseases in CSU patients is associated with higher disease activity (A, B), low total IgE levels (C), eosinophil (D) and basophil counts (E). The number of CSU patients: (A) n = 266 (AID+) and n = 777 (AID−); (B) total n = 230 (AID+) and total n = 684 (AID−); (C) n = 286 (AID+) and n = 789 (AID−); (D) n = 231 (AID+) and n = 749 (AID−); (E) n = 258 (AID+) and n = 768 (AID−).
AID, autoimmune disease; CSU, chronic spontaneous urticaria.

In patients with CSU, the presence of autoimmune diseases, mostly AITD, is associated with higher rates of hypothyroidism and hyperthyroidism

The majority (91%) of CSU patients had normal thyroid-stimulating hormone (TSH) levels (0.27–3.9 mU/L). Twenty-eight (4%) patients showed low (below 0.27 mU/L) and 34 (5%) patients had high normal/high (above 3.9 mU/L) TSH levels.

Of patients with high normal/high TSH levels, 68% (n = 23) had autoimmune diseases; of patients with low TSH levels, 54% (n = 15) had autoimmune diseases; of patients with normal TSH levels, only 24% (n = 143) had autoimmune diseases ($P < 0.001$ for all, **Table 3**). No difference regarding autoimmune diseases was seen between patients with low and elevated TSH levels.

Seventy-one percent (27/38) of patients with high normal/high or low TSH levels were diagnosed HT or had elevated IgG anti-TPO levels. One patient had Graves' disease and 7 patients had undefined AITD.

In patients with CSU, comorbid autoimmune diseases are linked to having type IIb autoimmune CSU

Patients with any of the definition criteria for aiCSU such as a positive ASST, BAT and/or BHRA more often had autoimmune diseases as compared to patients without (**Table 3**). Risk of having autoimmune diseases is 1.7, 2.9 and 3.3 times greater for CSU patients with positive ASST, BHRA and BAT as compared to CSU patients with negative results of ASST, BHRA and BAT, respectively. CSU patients with detectable IgG anti-FcεRIα/IgE showed similar rates of autoimmune diseases as patients without IgG anti-FcεRIα/IgE (**Table 3**).

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Table 4. Response to omalizumab therapy in chronic spontaneous urticaria patients with positive antinuclear antibodies and/or IgG anti-TPO

ANA and/or IgG anti-TPO, (No.)	Response to omalizumab, % (No.)			*P* value
	NR	PR	CR	
+ (20)	71.4 (5)	61.1 (11)	20 (4)	0.012*
– (25)	28.6 (2)	38.9 (7)	80 (16)	

TPO, thyroperoxidase; ANA, antinuclear antibodies; NR, non-responders; PR, partial responders; CR, complete responders; +, present; –, absent.
*Comparison between groups: NR vs. PR: $P = 0.68$, NR vs. CR: $P = 0.02$, PR vs. CR: $P = 0.019$.

The prevalence of autoimmune diseases was significantly higher in patients who had true 'triple-positive' aiCSU (60%) as compared to patients who were positive only for some but not all markers of aiCSU (28%) and patients who had 'triple-negative' CSU (17%, **Table 3**).

Other features of aiCSU, *i.e.* lower blood eosinophil and basophil counts and lower total IgE levels, were also linked to presence of autoimmune diseases in CSU patients (**Fig. 1C-E**, **Table 3**).

Markers for autoimmune diseases, in patients with CSU, are associated with poor treatment responses to omalizumab

In CSU patients, the prevalence of ANA and/or IgG anti-TPO positivity was significantly higher in non-responders to omalizumab treatment (71%, 5/7) as compared to complete responders (20%, 4/16, **Table 4**). ANA and/or IgG anti-TPO were negative in 80% of complete responders, 39% of partial responders and 29% of non-responders.

DISCUSSION

The results of our study confirm that around one-third of CSU patients have autoimmune comorbidities. Importantly, autoimmune comorbidity is strongly linked to type IIb aiCSU. These findings support the concept that aiCSU is a distinct endotype of CSU. They also help assess and monitor patients with CSU, especially those with aiCSU, for comorbid autoimmune diseases in routine clinical practice.

How common are autoimmune comorbidities in the general population and in patients with CSU? Most AID are rare or very rare diseases, whereas others, such as thyroiditis or type I diabetes, are more common. A recent population-based study involving ~800,000 individuals in Catalonia (Spain) investigated the prevalence of 78 autoimmune diseases and identified AITD with 5% as the most prevalent one, followed by type I diabetes and rheumatoid arthritis (both < 1%).[25] In our population of CSU patients (only a few patients were also from Catalonia), 25% had comorbid AITD, HT or Graves' disease, indicating that AITD is more than 5 times as common in CSU as in the normal population. This is in line with the results of numerous previous studies, which reported rates of HT to range from 1% to 28% in CSU.[17] In our study, vitiligo is also more prevalent in CSU patients as compared to the general population (2% vs. < 1%).[25] Furthermore, the prevalence of rheumatoid arthritis and autoimmune gastritis is likely to be higher in CSU (1% in our study) than in the general population (< 1%, **Table 1**).

In 2% of our patients, CSU was associated with 2 or 3 autoimmune diseases, mostly HT and vitiligo, autoimmune gastritis or rheumatoid arthritis, a so-called autoimmune polyglandular syndrome. This is in line with previous studies, where vitiligo and rheumatoid arthritis were also the most frequently reported autoimmune diseases in combination with AITD and CSU.[11,12,26,27]

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In CSU patients as well as in the general population, autoimmune diseases are associated with female sex, older age and having a family history of autoimmune diseases.[11,12,22,25,28] In 2 large retrospective studies, chronic urticaria in female patients was strongly associated with AITD, SLE, vitiligo, Henoch-Schönlein purpura,[29] rheumatoid arthritis, Sjögren syndrome, celiac disease and type I diabetes mellitus.[12] Autoimmune diseases that are more prevalent in children and young adults, *e.g.* celiac disease and diabetes mellitus type I,[22,28] are also more frequently observed in younger CSU patients of our cohort. Caminiti *et al.*[30] previously reported that the presence of celiac disease in children with chronic urticaria was significantly more frequent than in control children. However, an overall prevalence of autoimmune diseases is likely to be lower in young CSU patients than in middle-aged CSU patients.[17,31] This might be explained by the fact that autoimmunity, including autoimmune CSU, develops with age and that most autoimmune diseases appear 10 years after the onset of CSU.[12]

What are the clinical implications of our findings? AITD presents with euthyroidism or hypothyroidism in HT and hyperthyroidism (thyrotoxicosis) in Graves' disease. HT is linked to many other autoimmune diseases, for example, vitiligo.[26,32] IgG anti-TPO is considered a sensitive marker for both HT and Graves' disease. IgG anti-TPO appears in 90% of HT patients compared to 25%–50% for IgG anti-thyroglobulin.[33] In patients with HT, euthyroidism, *i.e.* IgG anti-TPO positivity, normal TSH and thyroid hormone levels, and absence of symptoms, or subclinical hypothyroidism can progress to overt hypothyroidism.[34] Increased rates of this progression are associated with female sex, TSH ≥ 7 mU/L and increased IgG anti-TPO titers.[33-36] The frequency of IgG anti-TPO positivity also increases with age, with a peak at around 50 years.[33]

Does this mean that adult CSU patients should be screened for IgG anti-TPO? Several independent lines of evidence support to do this and suggest that screening CSU patients for HT may improve outcomes of both HT and CSU. First, we and others detected an increased prevalence of HT diagnosed by serum levels of IgG anti-TPO in >10% of CSU patients. It was associated with female sex, older age and higher rates of hypothyroidism.[7,12,17] Hypothyroidism, including subclinical hypothyroidism, is known to be linked to an increased risk for cognitive impairment, cardiovascular events and mortality from coronary heart disease.[34] Levothyroxine treatment may improve the prognosis, decrease the risk of adverse cardiovascular events and prevent progression to overt hypothyroidism.[34] Secondly, in CSU patients, HT was shown to be associated with other organ-specific and/or systemic autoimmune diseases including autoimmune polyglandular syndromes.[12,33] Therefore, diagnosis of HT may help to suspect and reveal other autoimmune comorbidity. Thirdly, HT may hint to the presence of aiCSU, which is usually more severe and resistant to omalizumab treatment.[4,37,38] Furthermore, treatment of hypothyroidism with levothyroxine might be associated with improvement of CSU,[17,39] although some studies did not confirm this.[40]

The international urticaria guideline recommends that physicians assess CSU patients for thyroid hormones and autoantibodies in the extended diagnostic workup if indicated by history.[1] In light of the evidence presented above as well as the findings of the present study, we recommend that all adult CSU patients[7] be screened for IgG anti-TPO. If elevated levels are detected, thyroid function should be checked (*e.g.* TSH, free T4) and tests for aiCSU (*e.g.* ASST, BAT/BHRA) can be performed. If thyroid function is not impaired and symptoms are absent, patients should be followed up periodically to monitor for symptoms of hypothyroidism and to detect any rise in their TSH and/or development autoimmune diseases other than HT (**Fig. 2**).[34,41]

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① Ask all CSU patients for signs and symptoms of Hashimoto's thyroiditis

For example, fatigue, loss of energy, decreased appetite, cold intolerance, dry skin, hair loss, inability to concentrate, constipation, blurred vision and other

② Confirmation of euthyroidism, subclinical or overt hypothyroidism

	Symptoms are present	Symptoms are absent
Tests	IgG-anti-TPO, free T_4, TSH	Adult patients: IgG-anti-TPO
Normal	· Consider another diagnosis · Consider referral*	· Consider reassessment in 1–3 years if CSU persists
IgG-anti-TPO ↑	· Consider LT treatment · Consider referral*	· Free T_4, TSH · Consider testing for aiCSU
TSH ↑, free T_4 ↓		· Repeat measurement · Consider LT treatment · Consider referral*
TSH ↑, free T_4 N	· Consider repeat measurement in 2–4 weeks · Consider referral*	· Repeat free T_4 measurement · If TSH > 7.0 mU/L: consider referral* and LT treatment to reduce risk of CHD events

Fig. 2. General approach to the management of Hashimoto's thyroiditis and hypothyroidism in patients with CSU (modified from [34]).
CSU, chronic spontaneous urticaria; TPO, thyroperoxidase; TSH, thyroid-stimulating hormone; LT, levothyroxine; aiCSU, autoimmune chronic spontaneous urticaria; CHD, coronary heart disease.
*Referral to an endocrinologist.

Are comorbid autoimmune diseases in patients with CSU linked to type IIb autoimmunity? Our findings show that in CSU, the presence of comorbid autoimmune diseases and a positive family history of autoimmune diseases are associated with markers of aiCSU, *e.g.* 'triple positivity' and low total IgE, which is in line with previous findings.[4,12,42] This may be explained by the known co-occurrence of multiple autoimmune phenomena and autoimmune diseases. Our observations, on one hand, strengthen the evidence for the existence of a distinct autoimmune subtype of CSU. On the other hand, they indicate the need to include targeted questions in the history and/or further laboratory diagnostic workup of comorbid autoimmune diseases in a subgroup of CSU patients. This is especially true for patients who are positive to ASST, BHRA and/or BAT and have autoantibodies detected by immunoassay. Surprisingly, we did not see higher rates of autoimmune diseases in patients with presence of IgG anti-FcεRIα/IgE. This might be explained by the fact that these antibodies are nonfunctional in some patients and were also described in healthy people.[43]

Patients with aiCSU are likely to have a worse and slow response to omalizumab[38,44] and a good response to cyclosporine[45] and inhibition of Bruton's tyrosine kinase by fenebrutinib (Metz *et al.*, personal communication). Whether the presence of comorbid autoimmune diseases can also predict response to treatment in CSU patients is unknown. We found that the presence of ANA and/or IgG anti-TPO, markers for autoimmunity and autoimmune diseases, was associated with non-response to omalizumab treatment. This is in line with

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recently reported data from a cohort of Turkish CSU patients, where poor response to omalizumab treatment was also linked to ANA-positivity.[46] In addition, in small studies and reports, omalizumab was less effective in patients with CSU and IgG anti-TPO.[47,48] In other studies, cyclosporine was more effective in CSU patients with ASST and/or BHRA positivity and raised thyroid autoantibodies.[49,50]

The major strength of the current study is the inclusion of a large cohort of patients from 12 European centers and assessment of many parameters, including triple testing for aiCSU. The retrospective analysis is a limitation of our study. The data from the patients was extracted from different centers in different countries and it can be expected that the diagnosis, management and treatment of patients differ significantly among centers and countries. Moreover, we compared aiCSU patients with patients with non type IIb autoimmune CSU rather than those with type I autoimmune CSU. This is a limitation of this study and needs to be addressed by future studies. Importantly, such studies need to also compare patients with type I and type IIb autoimmune CSU with patients who have both type I and type IIb autoimmune CSU, a subpopulation of CSU patients that is currently ill characterized in terms of its rate and clinical characteristics.[51] In addition, the 3 markers for aiCSU, *i.e.* basophils tests, ASST and IgG anti-FcεRIα/IgE, were only analyzed, in combination, in the patients from the PURIST study. The therapeutic response to omalizumab was evaluated only in a small subgroup of patients. Finally, some of the routine analyses were not performed by a central laboratory, rather than the centers involved, which may have increased the heterogeneity of data.

In conclusion, autoimmune diseases, especially HT and vitiligo, are common in CSU and linked to aiCSU and poor response to treatment with omalizumab. In CSU patients, autoimmune diseases are often overlooked, usually occur as CSU persists, can be treated and prevented by early treatment, and treatment can have positive effects on CSU. Therefore, we recommend that CSU patients be assessed for features of aiCSU and be investigated, at the onset of their urticaria and at regular intervals, for comorbid autoimmune diseases. In all adult CSU patients, we strongly recommend a) checking for symptoms of autoimmune diseases and screening for IgG anti-TPO with annual reassessment of thyroid function in positive asymptomatic cases; and b) a follow-up on a regular basis of patients with aiCSU, especially female patients with HT and/or a positive family history, to screen for signs and symptoms of other autoimmune diseases.[11,41] Further studies are needed and should use additional markers for aiCSU, for example total IgE[52] or the ratio of IgG anti-TPO to total IgE, a recently reported marker for aiCSU.[4]

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SUPPLEMENTARY MATERIAL

Supplementary Table S1

Association between the presence of autoimmune diseases and clinical/laboratory parameters in patients with chronic spontaneous urticaria (within the groups of patients with or without autoimmune diseases)

Click here to view

REFERENCES

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-414.
PUBMED | CROSSREF
2. Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M. Immunoglobulin E-Mediated Autoimmunity. Front Immunol 2018;9:689.
PUBMED | CROSSREF
3. Bracken SJ, Abraham S, MacLeod AS. Autoimmune theories of chronic spontaneous urticaria. Front Immunol 2019;10:627.
PUBMED | CROSSREF
4. Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, E H Grattan C, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: results of the PURIST Study. Allergy 2019;74:2427-36.
PUBMED | CROSSREF
5. Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase--a novel pathomechanism of chronic spontaneous urticaria? PLoS One 2011;6:e14794.
PUBMED | CROSSREF
6. Sánchez J, Sánchez A, Cardona R. Causal relationship between anti-TPO IgE and chronic urticaria by *in vitro* and *in vivo* tests. Allergy Asthma Immunol Res 2019;11:29-42.
PUBMED | CROSSREF
7. Chanprapaph K, Iamsumang W, Wattanakrai P, Vachiramon V. Thyroid autoimmunity and autoimmunity in chronic spontaneous urticaria linked to disease severity, therapeutic response, and time to remission in patients with chronic spontaneous urticaria. BioMed Res Int 2018;2018:9856843.
PUBMED | CROSSREF
8. Altrichter S, Zampeli V, Ellrich A, Zhang K, Church MK, Maurer M. IgM and IgA in addition to IgG autoantibodies against FcεRIα are frequent and associated with disease markers of chronic spontaneous urticaria. Allergy 2020;75:3208-15.
PUBMED | CROSSREF
9. Konstantinou GN, Asero R, Ferrer M, Knol EF, Maurer M, Raap U, et al. EAACI taskforce position paper: evidence for autoimmune urticaria and proposal for defining diagnostic criteria. Allergy 2013;68:27-36.
PUBMED | CROSSREF
10. Maurer M, Eyerich K, Eyerich S, Ferrer M, Gutermuth J, Hartmann K, et al. Urticaria: collegium internationale allergologicum (CIA) update 2020. Int Arch Allergy Immunol 2020;181:321-33.
PUBMED | CROSSREF
11. Kolkhir P, Borzova E, Grattan C, Asero R, Pogorelov D, Maurer M. Autoimmune comorbidity in chronic spontaneous urticaria: a systematic review. Autoimmun Rev 2017;16:1196-208.
PUBMED | CROSSREF
12. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. J Allergy Clin Immunol 2012;129:1307-13.
PUBMED | CROSSREF
13. Gonzalez-Diaz SN, Sanchez-Borges M, Rangel-Gonzalez DM, Guzman-Avilan RI, Canseco-Villarreal JI, Arias-Cruz A. Chronic urticaria and thyroid pathology. World Allergy Organ J 2020;13:100101.
PUBMED | CROSSREF
14. Ghazanfar MN, Kibsgaard L, Thomsen SF, Vestergaard C. Risk of comorbidities in patients diagnosed with chronic urticaria: a nationwide registry-study. World Allergy Organ J 2020;13:100097.
PUBMED | CROSSREF

15. Zhao J, Wang C, Xu X, Zhang Y, Ren H, Ren Z, et al. Coexistence of autoimmune encephalitis and other systemic autoimmune diseases. Front Neurol 2019;10:1142.
PUBMED | CROSSREF

16. Magen E, Chikovani T, Waitman DA, Kahan NR. Association of alopecia areata with atopic dermatitis and chronic spontaneous urticaria. Allergy Asthma Proc 2018;39:96-102.
PUBMED | CROSSREF

17. Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: a systematic review. Allergy 2017;72:1440-60.
PUBMED | CROSSREF

18. Hasni S, Gupta S, Davis M, Poncio E, Temesgen-Oyelakin Y, Joyal E, et al. Safety and tolerability of omalizumab: a randomized clinical trial of humanized anti-IgE monoclonal antibody in systemic lupus erythematosus. Arthritis Rheumatol 2019;71:1135-40.
PUBMED | CROSSREF

19. Kremer N, Snast I, Cohen ES, Hodak E, Mimouni D, Lapidoth M, et al. Rituximab and omalizumab for the treatment of bullous pemphigoid: a systematic review of the literature. Am J Clin Dermatol 2019;20:209-16.
PUBMED | CROSSREF

20. Basta F, Mazzuca C, Nucera E, Schiavino D, Afeltra A, Antonelli Incalzi R. Omalizumab in eosinophilic granulomatosis with polyangiitis: friend or foe? A systematic literature review. Clin Exp Rheumatol 2020;38 Suppl 124:214-220.
PUBMED

21. Császár T, Patakfalvi A. Treatment of polyglandular autoimmune syndrome with cyclosporin-A. Acta Med Hung 1992-1993;49:187-93.
PUBMED

22. Hayter SM, Cook MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. Autoimmun Rev 2012;11:754-65.
PUBMED | CROSSREF

23. Stull DE, McBride D, Gimenez-Arnau A, Grattan C, Khalil S, Balp MM. Categorical health states in chronic spontaneous urticaria (Csu) based on the weekly urticaria activity score (Uas7): are they distinct, discriminative, and reproducible? Value Health 2014;17:A611.
PUBMED | CROSSREF

24. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA(2) LEN task force consensus report: the autologous serum skin test in urticaria. Allergy 2009;64:1256-68.
PUBMED | CROSSREF

25. Sisó-Almirall A, Kostov B, Martínez-Carbonell E, Brito-Zerón P, Ramirez PB, Acar-Denizli N, et al. The prevalence of 78 autoimmune diseases in Catalonia (MASCAT-PADRIS Big Data Project). Autoimmun Rev 2020;19:102448.
PUBMED | CROSSREF

26. Fan KC, Yang TH, Huang YC. Vitiligo and thyroid disease: a systematic review and meta-analysis. Eur J Dermatol 2018;28:750-63.
PUBMED

27. Rams A, Żółciński M, Zastrzeżyńska W, Polański S, Serafin A, Wilańska J, et al. Autoimmune polyendocrine syndrome type 2 in patient with severe allergic asthma treated with omalizumab. J Asthma 2018;55:1384-6.
PUBMED | CROSSREF

28. Ruggeri RM, Trimarchi F, Giuffrida G, Certo R, Cama E, Campennì A, et al. Autoimmune comorbidities in Hashimoto's thyroiditis: different patterns of association in adulthood and childhood/adolescence. Eur J Endocrinol 2017;176:133-41.
PUBMED | CROSSREF

29. Chiu HY, Muo CH, Sung FC. Associations of chronic urticaria with atopic and autoimmune comorbidities: a nationwide population-based study. Int J Dermatol 2018;57:822-9.
PUBMED | CROSSREF

30. Caminiti L, Passalacqua G, Magazzù G, Comisi F, Vita D, Barberio G, et al. Chronic urticaria and associated coeliac disease in children: a case-control study. Pediatr Allergy Immunol 2005;16:428-32.
PUBMED | CROSSREF

31. Kosmeri C, Siomou E, Challa A, Tsabouri S. Investigation of autoimmune disease in children with chronic spontaneous urticaria. Int Arch Allergy Immunol 2019;180:250-4.
PUBMED | CROSSREF

32. Yuan J, Sun C, Jiang S, Lu Y, Zhang Y, Gao XH, et al. The prevalence of thyroid disorders in patients with vitiligo: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2019;9:803.
PUBMED | CROSSREF

33. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmun Rev 2015;14:174-80.
PUBMED | CROSSREF

34. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA 2019;322:153-60.
PUBMED | CROSSREF

35. Li Y, Teng D, Shan Z, Teng X, Guan H, Yu X, et al. Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. J Clin Endocrinol Metab 2008;93:1751-7.
PUBMED | CROSSREF

36. Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab 2010;95:1095-104.
PUBMED | CROSSREF

37. Kolkhir P, Church MK, Altrichter S, Skov PS, Hawro T, Frischbutter S, et al. Eosinopenia, in chronic spontaneous urticaria, is associated with high disease activity, autoimmunity, and poor response to treatment. J Allergy Clin Immunol Pract 2020;8:318-325.e5.
PUBMED | CROSSREF

38. Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. J Allergy Clin Immunol 2017;139:1059-1061.e1.
PUBMED | CROSSREF

39. Shahbaz A, Senapathi SH, Aziz K, Umair M, Khalid A, Sachmechi I. Improvement of chronic idiopathic urticaria with levothyroxine: a case report and review of literature. Cureus 2018;10:e3209.
PUBMED | CROSSREF

40. Magen E, Mishal J. The effect of L-thyroxine treatment on chronic idiopathic urticaria and autoimmune thyroiditis. Int J Dermatol 2012;51:94-7.
PUBMED | CROSSREF

41. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. J Clin Endocrinol Metab 2003;88:2983-92.
PUBMED | CROSSREF

42. Sánchez J, Sánchez A, Cardona R. Clinical characterization of patients with chronic spontaneous urticaria according to anti-TPO IgE levels. J Immunol Res 2019;2019:4202145.
PUBMED | CROSSREF

43. Ulambayar B, Chen YH, Ban GY, Lee JH, Jung CG, Yang EM, et al. Detection of circulating IgG autoantibody to FcεRIα in sera from chronic spontaneous urticaria patients. J Microbiol Immunol Infect 2020;53:141-7.
PUBMED | CROSSREF

44. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. Allergy 2018;73:705-12.
PUBMED | CROSSREF

45. Kulthanan K, Subchookul C, Hunnangkul S, Chularojanamontri L, Tuchinda P. Factors predicting the response to cyclosporin treatment in patients with chronic spontaneous urticaria: a systematic review. Allergy Asthma Immunol Res 2019;11:736-55.
PUBMED | CROSSREF

46. Ertaş R, Hawro T, Altrichter S, Özyurt K, Erol K, Ketenci Ertaş Ş, et al. Antinuclear antibodies are common and linked to poor response to omalizumab treatment in patients with CSU. Allergy 2020;75:468-70.
PUBMED | CROSSREF

47. Türk M, Yılmaz İ, Bahçecioğlu SN. Treatment and retreatment with omalizumab in chronic spontaneous urticaria: real life experience with twenty-five patients. Allergol Int 2018;67:85-9.
PUBMED | CROSSREF

48. Cordeiro Moreira AS, Rosmaninho Lopes de Soares E Silva MI, Pereira Guilherme MA, da Silva Ferreira JA, Fonseca Moreira da Silva JP. Use of omalizumab in the treatment of chronic urticaria. Eur Ann Allergy Clin Immunol 2016;48:242-6.
PUBMED

49. Kolkhir P, Pogorelov D, Kochergin N. Chronic spontaneous urticaria associated with vitiligo and thyroiditis (autoimmune polyglandular syndrome IIIC): case series. Int J Dermatol 2017;56:e89-90.
PUBMED | CROSSREF

50. Iqbal K, Bhargava K, Skov PS, Falkencrone S, Grattan CE. A positive serum basophil histamine release assay is a marker for ciclosporin-responsiveness in patients with chronic spontaneous urticaria. Clin Transl Allergy 2012;2:19.
PUBMED | CROSSREF

51. Asero R, Marzano AV, Ferrucci S, Lorini M, Carbonelli V, Cugno M. Co-occurrence of IgE and IgG autoantibodies in patients with chronic spontaneous urticaria. Clin Exp Immunol 2020;200:242-9.
PUBMED | CROSSREF

52. Altrichter S, Fok JS, Jiao Q, Kolkhir P, Pyatilova P, Romero SM, et al. Total IgE as a marker for chronic spontaneous urticaria. Allergy Asthma Immunol Res 2021;13:206-18.
PUBMED | CROSSREF

53. Benigno M, Anastassopoulos KP, Mostaghimi A, Udall M, Daniel SR, Cappelleri JC, et al. A large cross-sectional survey study of the prevalence of alopecia areata in the United States. Clin Cosmet Investig Dermatol 2020;13:259-66.
PUBMED | CROSSREF