Chronic Spontaneous Urticaria

6

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6.1 Definition

Chronic spontaneous urticaria (CSU) is characterized by the rapid and unprompted appearance of itchy weals and/or angio-oedema. Weals are short-lived superficial skin swellings of variable size that are associated with itching or burning (Fig. 6.1). Weals come with flare reactions of the surrounding skin, and they resolve spontaneously (usually within several hours). Angio-oedemas are sudden, deeper, pronounced, and sometimes painful swellings of the lower dermis and subcutis. They are of longer duration and slower resolution than weals (usually several hours to a few days) (Fig. 6.2). The signs and symptoms of CSU occur spontaneously, seemingly "out of the blue," and it is usually impossible to predict when, why, and where they will appear next. This makes CSU unique. In all other forms of chronic urticaria, definite triggers (Table 6.1) induce the signs and symptoms.

6.2 Clinical Picture

Several studies have looked at the patterns of occurrence of weals and angio-oedema in CSU patients. A representative cross-sectional population survey conducted in Germany included 4093 individuals with urticaria. Of the included patients with CSU, 33% had weals and angio-oedema, and 61% and 6%, respectively, exclusively had weals and angio-oedema [1]. A more recent study included 673 patients primarily from hospital-based specialist centers. Within these patients with CSU from

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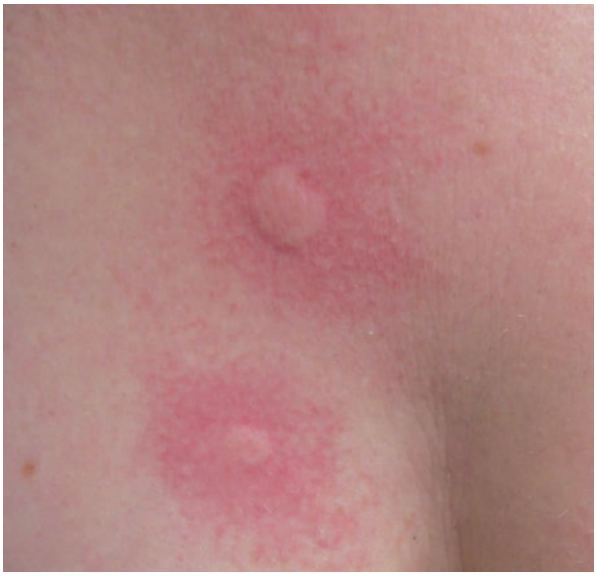

Fig. 6.1 Weal and flare type skin reactions in CU patient

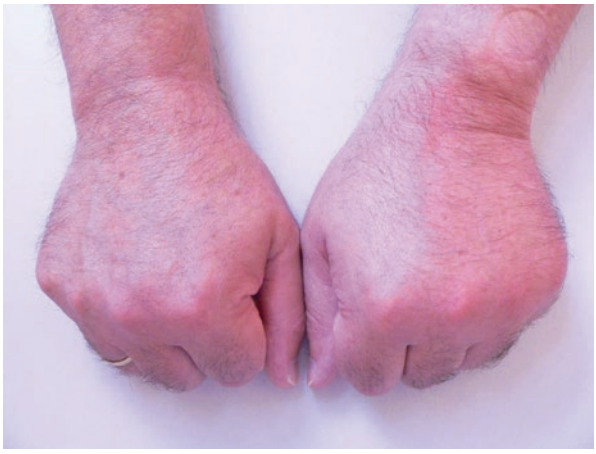

Fig. 6.2 Angio-oedema of the left hand in CU patient

Canada, France, Germany, Italy, Spain, the Netherlands, and the United Kingdom 59% had both weals and angio-oedema [2]. Another recent study found 50% of CSU patients had weals and angio-oedema, about 1 in 3 CSU patients had only weals, and 1 in 10 patients had only angio-oedema [3]. In pediatric patients with CSU, 5–14% were found to have angio-oedema [4].

The signs and symptoms of CSU can occur at anytime and anywhere on the skin. Most often, however, weals develop during the evening hours favoring the arms and legs [5], whereas angio-oedema is most commonly located in the head region (e.g., eye lids, lips, tongue) as well as hands and feet [1]. In most patients with moderate or severe CSU, weals and/or angio-oedema occur every or almost every day [6]. In

Table 6.1 Classification of chronic urticaria

Chronic urticaria	
Chronic spontaneous urticaria	Inducible urticaria
Spontaneous appearance of weals, angio-oedema or both for >6 weeks	Symptomatic dermographism (also called Urticaria factitia/dermographic urticaria)
	Cold urticaria (also called cold contact urticaria)
	Solar urticaria
	Delayed pressure urticaria
	Heat contact urticaria
	Vibratory angio-oedema
	Cholinergic urticaria
	Contact urticaria
	Aquagenic urticaria

Adapted from Zuberbier et al. (2017)

the same patient, disease activity can change markedly over time. Periods of weeks and months, in which no or very few signs and symptoms occur, can alternate with other times, in which disease activity is high. In some patients, unspecific triggers such as stress or infections can sporadically lead to exacerbation of CSU.

CSU is of long duration in most patients, about 50% of patients with CSU are affected for more than 10 years [6, 7] although others show more rapid resolution, and the average duration of CSU is held to range from 4 to 7 years. CSU shows spontaneous remission in virtually all patients [6, 8–10]. It is expected that cases presenting to specialist clinics are likely to be more severe and prolonged than those that are managed in the community.

6.3 Epidemiology

CU is a common condition in all parts of the world. Lifetime prevalence for CSU was found to be around 2% [1]. Women are consistently found to suffer at least twice as often from CSU as men [1]. The peak age bracket of disease onset is 20–60 years in both [6], but CSU can occur at any age. The estimated 1 year interval prevalence of CSU in pediatric patients was 0.75% in a physician-based on-line survey [4] and thus similar to adults. CSU may be more common in Asia and South America as compared to North America and Europe, and the prevalence appears to be increasing [11].

6.4 Etiopathogenesis

The signs and symptoms of CSU are brought about by the activation of cutaneous mast cells [12]. Mast cells are large resident skin cells with characteristic metachromatic cytoplasmic granules that contain preformed mediators such as histamine. Mast cells are preferentially localized in the vicinity of sensory nerves and small

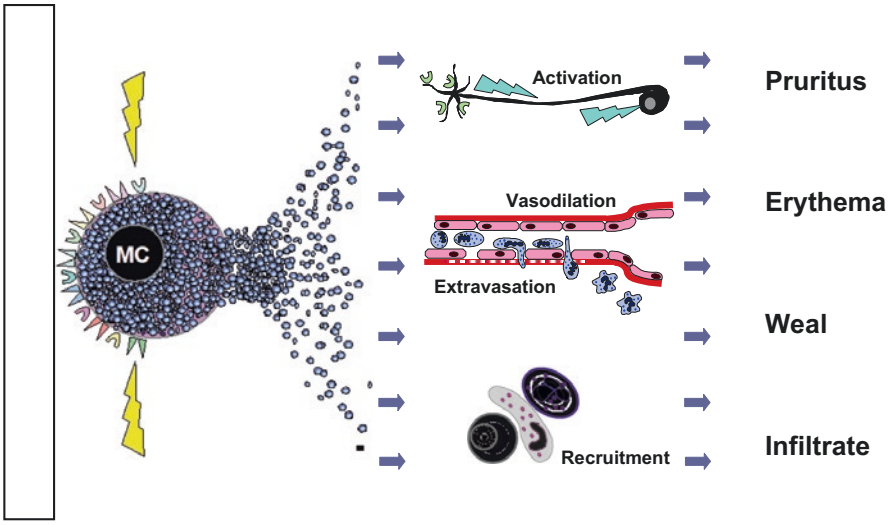

Fig. 6.3 Mast cell degranulation and its effects in CU

blood vessels of the dermis. Their main physiological role is to provide a first line of defense against pathogens and other environmental dangers [13]. Mast cell degranulation and the subsequent release of mediators including histamine induce sensory nerve stimulation (pruritus) and vasodilatation (erythema), increased extravasation (edema) as well the recruitment of eosinophils, basophils, neutrophils, and other immune cells (infiltrate) (Fig. 6.3). Mast cell degranulation and its modulation are a complex process that can involve a large range and number of receptor–ligand interactions (Fig. 6.4). In CSU patients, two different types of autoimmune mechanisms are held to be relevant for the degranulation of skin mast cells, IgE-mediated auto-allergic activation, and IgG-mediated type IIb autoimmune activation [14].

6.4.1 Autoallergy and Autoimmunity, Causes of CSU

Autoallergy describes the phenomenon of type I hypersensitivity to self, in which antigens crosslink IgE autoantibodies bound to the high affinity IgE receptor on mast cells and basophils to cause their degranulation. CSU characterized by functional IgE autoantibodies is referred to as auto-allergic or type I autoimmune CSU. IgE against autoantigens is found and held to contribute to CSU pathogenesis in more than two-thirds of patients with CSU. Half of CSU patients were found to have elevated levels of IgE autoantibodies against thyreoperoxidase [15], and 70% of CSU patients had IgE autoantibodies against interleukin-24 (IL-24) [16]. Recent studies showed that IgE autoantibodies of CSU patients are directed to a wide variety of autoantigens, many of which are expressed in the skin. These include IL-24,

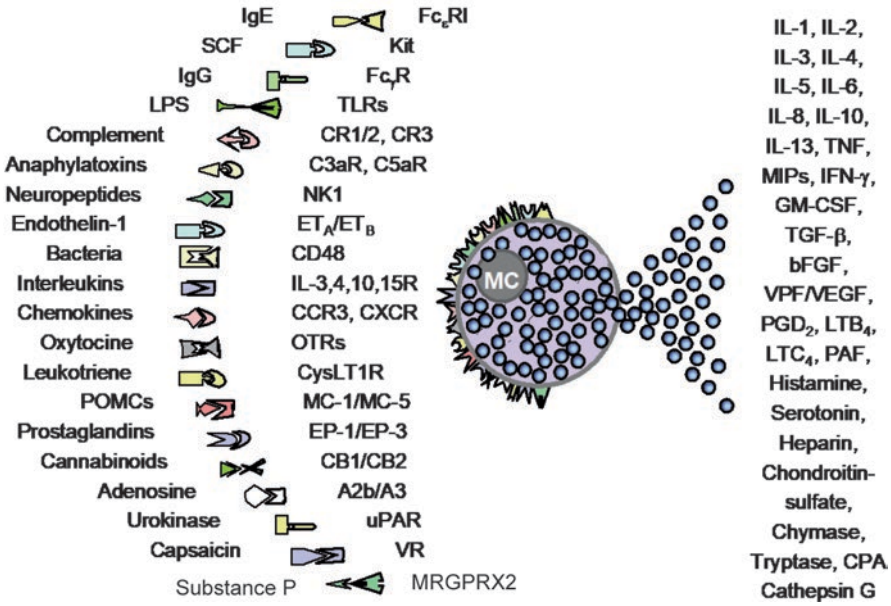

Fig. 6.4 Selection of receptor–ligand interactions resulting in mast cell activation

which is often recognized by IgE of CSU patients and which is functionally relevant. IgE anti-IL-24 and IL-24 together lead to the degranulation of mast cells [16]. The IgE anti-IL-24 levels of urticaria patients correlate with their disease activity. Furthermore, it has been shown that IgE autoantibodies are responsible for the increased total IgE levels in CSU patients and that the overall IgE of CSU patients is mostly directed against autoantigens [16] Recently, the relevance of IgE-anti-TPO in the pathogenesis of auto-allergic CSU has been demonstrated *in vivo*, by adoptive transfer of patient serum [17].

The therapeutic success of omalizumab in CSU provides further evidence for the relevance of IgE autoantibodies for the pathogenesis of CSU. The first ever placebo-controlled multicentric study with omalizumab in CSU showed very rapid improvement and very high rates of response (70% complete responders). Only patients with IgE against thyroid thyreoperoxidase were treated in this study [8].

6.4.2 Autoimmunity

Type IIb autoimmunity describes a hypersensitivity reaction to self in which antibodies, usually IgG or IgM, bind to antigen on a target cell, which then leads to the activation of this target cell. In a subpopulation of CSU patients, type IIb autoimmunity, i.e., IgG autoantibodies to IgE or its high affinity receptor, FceRI, is held to be the underlying cause. Functional IgG autoantibodies to the alpha-chain of FceRI are found in 20–30% of all patients with CSU. The prevalence of IgG

autoantibodies to IgE is significantly lower. IgG autoantibodies to IgE or the IgE receptor can be functional and degranulate mast cells, *in vitro* and *in vivo* [18, 19].

About 50% of patients with autoreactivity (a positive autologous serum skin test) have functional autoantibodies as evidence of type IIb autoimmune urticaria. To perform a positive Autologous Serum Skin Test (ASST), serum of the patient is injected intradermally and induces a weal-and-flare response [20]. Other tests such as the Basophil Histamine Release Assay, BHRA, or the Basophil Activation Test, BAT, are more specific than the ASST to screen for type IIb autoimmune CSU. Herein, the serum of CSU patients is incubated with basophils of healthy individuals. If histamine release or activation of basophils occurs, this points to the presence of IgG autoantibodies [21]. Numerous studies suggest that CSU patients with IgG-mediated type IIb autoimmune urticaria have a longer duration of illness, a higher likelihood of developing angio-oedema, increased disease activity, and more frequent autoimmune comorbidities [14, 21, 22]. It has recently been shown that CSU patients with features of type IIb autoimmune CSU have a different and most importantly delayed response to omalizumab therapy [23, 24].

6.4.3 Stress, Infections, and Food Intolerance, Modulators of CSU

Stress, infections, and foods can be relevant modulators of mast cell activation and CSU disease activity. Many CSU patients know that stress makes their disease worse. Several neuropeptides, such as Substance P (SP), released during stress reactions have mast cell modulating effects. SP is upregulated in the serum of patients with CSU patients and is linked to disease activity [25]. Weal reactions to intradermally injected neuropeptides such as SP are larger and longer lasting in CSU patients. SP acts on mast cell via binding to MRGPRX2 [26], which has been reported to be strongly expressed by skin mast cells in CSU.

Clinical experience shows that the treatment of chronic infections can lead to an improvement in CSU. In the context of persistent bacterial infections, bacterial components and components of the immune system (for example, complement factors) act on mast cells. Infections that can modulate CSU activity include bacterial infections, e.g., of the nasopharynx or by Helicobacter pylori of the gastrointestinal tract, and parasite infections, e.g., with Blastocystis hominis [27–29]. Mast cells have been shown in murine models to protect the host from pathogen invasion and from the pathology associated with bacterial infections, and mast cells are equipped with multiple surface receptors that function as sensors for pathogens. These include toll like receptors, complement receptors, and Fc receptors. Which of these mechanisms are relevant for the activation of mast cells in patients with CSU who have infections remains unclear. Also, there are very few controlled trials on the role and relevance of chronic infections in CSU patients. Generally, CSU patients do not exhibit an increased prevalence of infections, and infections should only be regarded as relevant in patients who show CSU improvement or remission upon successful

eradication of the infectious pathogen. The most common bacterial infection linked to CSU is *Helicobacter pylori*-gastritis. Parasite infections (e.g., by *Toxocara canis*, *Giardia lamblia*, or *Blastocystis hominis*) rarely contribute to CSU in Northern European countries, but are more frequent in other regions of the world. Intestinal candidosis used to be regarded as a common underlying cause for CSU [30], but more recent findings do not support this view [31]. Nevertheless, it is recommended that symptomatic candidosis is treated, especially in sensitized patients identified by intracutaneous testing.

CSU patients frequently suspect that their symptoms are brought about by the food they eat [32]. This can be indicative of CSU exacerbation due to intolerance, i.e., non-allergic, dose dependent, and delayed (4–12 h) onset hypersensitivity to food pseudoallergens such as food colorants, preservatives, taste intensifiers, and naturally occurring substances, e.g., aromatic compounds, biogenic amines, and salicylic acid. A role of intolerance in patients with CSU is supported by decreased disease activity following a 3–4 week diet low in pseudoallergens and increased disease activity following challenge tests with pseudoallergens. Responder rates vary and range from 50 to 90% following elimination and from 20 to 60% following challenge testing [33]. Many pseudoallergens are known to alter the activation threshold of mast cells for subsequent degranulation, but they themselves have no degranulating effects.

Skin mast cells express numerous G protein-coupled receptors (GPCRs), which are the largest group of membrane receptor proteins and common targets of drug therapy. Many compounds including some neuropeptides, antimicrobial peptides, and drugs activate human skin mast cells through a GPCR known as Mas-related G protein-coupled receptor X2 (MRGPRX2) [34]. MRGPRX2 may play an important role in the pathogenesis of CSU [26].

6.5 Diagnostic Workup

Spontaneously recurring weals and/or angio-oedema occur not only in patients with CSU. Several differential diagnoses need to be ruled out, by a thorough history and follow up diagnostic tests if indicated. Recurrent weals without angio-oedema occur in urticaria vasculitis and autoinflammatory disorders such as Schnitzler syndrome or cryopyrin-associated periodic syndromes (CAPS). Patients who exclusively develop recurrent angio-oedema, but not weals, may have bradykinin-mediated angio-oedema, e.g., angiotensin-converting-enzyme (ACE)-inhibitor induced angio-oedema or hereditary angio-oedema.

Once the diagnosis of chronic urticaria has been established, it is important to determine which form or forms of chronic urticaria the patient is suffering from. Individuals affected by the various forms of chronic inducible urticaria report that they can deliberately trigger weals or angio-oedema by exposing themselves to the relevant triggers, while patients with CSU cannot.

History taking is indispensable in patients with CSU. In addition to ruling out differential diagnoses, the history should explore comorbidities, markers of disease

Table 6.2 Chronic urticaria—Questions that should be asked…

1	When did your urticaria first present? (Life events?)
2	How often do you have weals and how long do they last?
3	When during the day are the weals most itchy?
4	What is the usual shape and size of weals and what skin areas are affected?
5	Do you get angio-oedema? How often? Where? For how long?
6	What problems do the weals/angio-oedema cause? (e.g., itch/pain/burning?)
7	Does or did anyone in your family also suffer from urticaria (or allergies)?
8	Do you have allergies/other diseases? What do you think is the cause?
9	Can you induce the onset of weals/angio-oedema, e.g., rubbing of the skin?
10	What drugs do you use (NSAIDs, hormones, laxatives, alternative remedies)?
11	Do you see a relationship of weal/angio-oedema onset and the food you eat?
12	Do you smoke/drink alcohol? Do you see a relationship?
13	What type of work do you do? Do you see a relationship?
14	What do you do for fun? Do you see a relationship?
15	Does your urticaria change on the weekend/during holidays or vacation?
16	Do you react normally to insect stings/bites (e.g., bees, yellow jackets)?
17	What therapies have you tried and what were the results?
18	Does stress trigger weals?
19	Is your quality of life affected by the urticaria? How?
20	In female patients: do you see a relationship with your menstrual cycle?

course and activity, and predictors of response to treatment. In patients with long-lasting and uncontrolled disease, further diagnostic steps to identify relevant drivers of disease activity should be considered and taken if indicated. These steps should be based on a thorough history, taking the following questions into consideration (Table 6.2).

In all patients with CSU, initial laboratory tests should include erythrocyte sedimentation rate and/or C-reactive protein as well as a differential blood count. While the goal of these tests is to rule out systemic inflammatory events, CSU, by itself, may lead to elevated levels. Depending on the history and the duration and severity of CSU, patients should subsequently undergo further diagnostic workup for causes and associated disorders. Exhaustive and pricy general screening programs for causes of urticaria are strongly advised against.

Whereas type I allergy is hardly ever a cause of CSU, non-allergic hypersensitivity reactions to NSAIDs or food may be more relevant for CSU. Bacterial, viral, parasitic, or fungal infections, e.g., with *H. pylori,* streptococci*,* staphylococci*, Yersinia, Giardia lamblia, Mycoplasma pneumoniae*, hepatitis viruses*, norovirus, parvovirus B19, Anisakis simplex, Entamoeba* spp*, Blastocystis* spp, have been implicated as potential causes of urticaria [35]. More data on the role of infections in modulating CSU disease activity is needed in order to make definitive recommendations. Ruling out malignancies is necessary if patient history (e.g., sudden loss of weight) points to this, routine screening is not suggested.

Basophil tests (BTs) and the Autologous Serum Skin Test (ASST) are the only generally available tests to screen for autoantibodies against IgE or against the high affinity IgE receptor (FcεR1). Histamine release or activation of donor basophils

after stimulation with the serum of CSU patients is measured by BTs. BTs also help to diagnose autoimmune urticaria [36], co-assess disease activity [37], and to predict the response to ciclosporin A or omalizumab [24, 38]. The ASST evaluates the presence of vasoactive factors and a heightened responsiveness of skin during active urticaria to stimulation [20, 21].

In order to guide treatment decisions, to understand and assess the patients' disease burden, and to better document the patient's history, patient-reported outcome (PRO) measures should be used in the diagnostic workup of CSU. As most of CSU patients show a great variability in daily symptoms, the use of these tools is highly recommended. Disease activity should be assessed with the urticaria activity score (UAS) and the angio-oedema activity score (AAS). Patients record and quantify their symptoms (UAS: weals and pruritus, AAS: angio-oedema) on a daily basis. Disease control is assessed by use of the urticaria control test (UCT) and angio-oedema control test (AECT). The UCT and the AECT allow patients and their physicians to rapidly and reliably measure retrospectively disease control with four simple questions each. Quality of life impairment is determined with the chronic urticaria quality of life questionnaire (CU-Q2oL) and the angio-oedema quality of life questionnaire (AE-QoL).

In everyday clinical practice, assessment of disease burden, activity and control simplifies treatment decision making.

6.6 Therapy

CSU in most patients cannot be cured, as no causal treatment is available as of yet to eliminate the underlying autoimmunity or autoallergy. The goal of therapeutic approaches in CSU, therefore, is for patients to gain complete control of all signs and symptoms, to be free of weals and angio-oedema, until spontaneous remission occurs. All patients should avoid known triggers, such as nonsteroidal anti-inflammatory drugs. In addition, prophylactic symptomatic medication is recommended for all patients.

The first line treatment for CSU is a non-sedating H1-antihistamine of the second generation [39]. Patient-reported outcome measures such as the UAS, the AAS, the UCT, and/or the AECT should be used to monitor the response to this treatment. Initially, the antihistamine shall be taken at the approved standard dose of once daily. It is important to explain to patients the benefits of the regular use of antihistamines, so that they do not take them only once symptoms occur. Patients who still develop weals or angio-oedema after two to four weeks of the daily use of a standard-dosed H1-antihistamine should increase their dose of this antihistamine to up to fourfold of the standard dose. For many non-sedating antihistamines, updosing has been shown to be efficient and safe and well tolerated [40].

Patients who still have no control over their CSU with a higher than standard-dosed non-sedating H1-antihistamine should be treated with add on omalizumab. This recombinant humanized anti-IgE antibody is administered by subcutaneous injection at the standard dose of 300 mg every 4 weeks. Safety and efficacy of

omalizumab in the treatment of patients with CSU were shown in clinical studies and in everyday use [41, 42]. Several mechanisms have been suggested to add to the therapeutic response of omalizumab in patients with CSU as well as to the heterogeneity of their clinical reactions [24, 43–45].

Most patients show a strong response even before the second dose [46, 47]. Some patients require multiple doses to achieve treatment success [24]. If, after 6 months of treatment, the effects of omalizumab are still limited, off-label treatment with cyclosporine is suggested [39]. Placebo-controlled trials have confirmed the efficacy of cyclosporine in CSU [48]. There is also potential value of low-evidence drugs such as dapsone, sulphasalazine, methotrexate, mycophenolate mofetil, doxepin, montelukast, H2 antihistamines, and others [39]. They are widely used internationally and can be effective even though well-designed double-blind studies may not be available.

Patients who have complete control of their symptoms should be checked for a complete remission of their CSU every 6–12 months.

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Chronic Spontaneous Urticaria and Comorbidities

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7.1 Introduction

Chronic spontaneous urticaria (CSU) affects up to 1% of the population [1, 2] and frequently coexists with other diseases, i.e., comorbidities. Comorbidities, in CSU patients, are important for several reasons.

Firstly, some comorbidities, e.g., autoimmune diseases (AIDs), are more common in CSU patients, and CSU patients may benefit from screening for these conditions [3, 4]. For example, high values of ESR, C-reactive protein (CRP), and/ or antithyroid antibodies may point to the presence of autoimmune thyroid disease (AITD) in a CSU patient [5]. Furthermore, there is increasing evidence that other CSU comorbidities such as metabolic syndrome (MS) and mental disorders are more prevalent and under-recognized in CSU [6]. As of yet, urticaria guidelines do not provide specific diagnostic recommendations on screening for these comorbidities [5].

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