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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Secondly, CSU comorbidities, for instance, mental disorders and chronic inducible urticarias (CIndUs), add to the burden of disease and quality of life impairment. Their identification and treatment, in clinical practice, can help to optimize the management of CSU patients.

Thirdly, some diseases, namely CIndUs and AITD, were suggested to be markers of longer CSU duration and progression from acute spontaneous urticaria to CSU [7–13].

Finally, certain diseases are linked, pathogenetically, to CSU, although the mechanisms are yet to be defined. Investigation of these diseases can help to better understand CSU, and their treatment can reduce CSU disease activity. In particular, some case reports supported this notion showing CSU remission or improvement after the treatment of malignancy, infection, and hyper- and hypothyroidism [14–16].

Here, we describe important groups of comorbidities of CSU, their prevalence, and their relevance for clinical practice.

7.2 Chronic Inducible Urticaria

CIndU is characterized by wheals and/or angioedema induced by exposure to external stimuli. CIndUs are classified as physical CIndUs (e.g., due to cold, heat, pressure, and other stimuli) and other types of CIndUs (cholinergic, aquagenic, and contact urticarias). CIndUs have been reported in 1–11% of the general population [17, 18] with symptomatic dermographism being the most prevalent type of physical CIndU (1–5%) and cholinergic urticaria being the most prevalent of other types

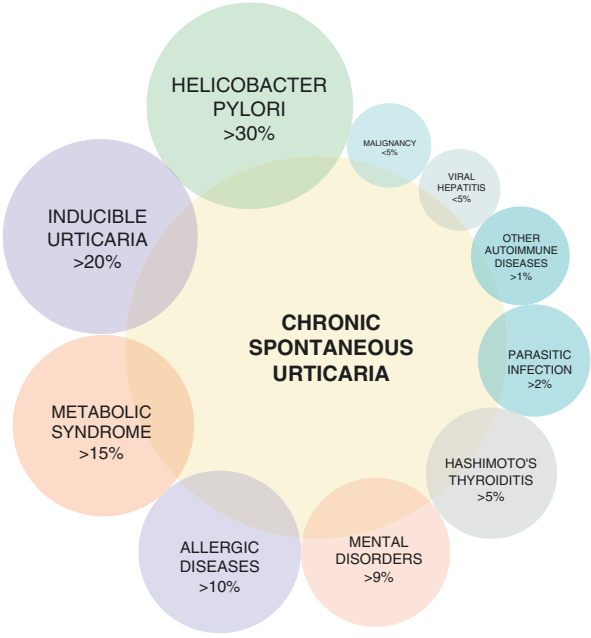

Fig. 7.1 The prevalence of comorbid diseases in CSU

of CIndU (4–11%) [18]. In a meta-analysis, CIndU was observed in 13% among all cases of chronic urticaria [19]. In other studies, 11–75% of CSU patients had comorbid CIndU, with most studies reporting rates of >20% (Fig. 7.1) [7–9, 20–24].

CSU primarily occurs in combination with delayed pressure urticaria (DPU, 2–37%), symptomatic dermographism (SD, 5–75%), cold urticaria (1–13%), and cholinergic urticaria (2–18%). Aquagenic urticaria (0.4%) [7–9, 20, 21, 23, 24], solar urticaria (0.4–0.5%), heat contact urticaria (0.2–4.3%), and vibratory urticaria/angioedema (0.1%) are rare in CSU [17, 24]. Two or more types of CIndU can be present in the same CSU patient [21].

Some CSU patients report that physical and other external stimuli can exacerbate or trigger symptom development. However, CIndU should only be diagnosed when provocation testing is positive. In one study, only half of the 186 patients with CSU, who reported that a physical trigger is relevant, had a positive challenge test result [21]. In the literature, it is not always clear that comorbidity rates reported are based on provocation testing, in fact in some cases it is clear that they are not. Therefore, larger studies of CSU patients subjected to CIndU provocation testing are needed.

Most CIndUs, on average, are of longer duration than CSU [10, 11]. After 10 years, only 26 ± 7% of patients with cold urticaria and 36 ± 10% of patients with cholinergic urticaria exhibited spontaneous remission in comparison to 49 ± 4% of CSU patients [11]. Importantly, CSU is of longer duration when in combination with CIndU [7, 9] (Table 7.1). In one study, rates of remission after 1 year were 21% and 47% for CSU patients with and without CIndU, respectively [7]. SD appears to be an exception. One year spontaneous remission rates of SD patients are similar to those of CSU patients (51 ± 6%), and comorbid SD is not associated with a longer duration of CSU [8, 11].

CSU patients with CIndU may also show higher CSU disease activity as assessed by urticaria activity score, higher rates of a personal history of atopy, and younger age, compared to CSU patients without CIndU [9]. Several studies suggest that CIndU comorbidity is linked to a poor response to antihistamine (AH) treatment. Patients with CSU and CIndU more frequently needed therapy 5 years after the onset of disease and higher doses of second-generation AHs (sgAHs) as compared to patients with CSU only [9]. Moreover, AH-resistant CSU patients show a significantly higher incidence of concomitant CIndU (SD and/or DPU) [27]. In addition, in a multicenter study, CIndU was the most common comorbidity of sgAHs-refractory CSU [24]. In another study, SD and other CIndUs were markers of overall poor treatment control of CSU [28].

In summary, CIndU is a prevalent comorbidity of CSU patients, and SD and DPU appear to be the most common comorbid CIndUs. The presence of CIndU in CSU patients is likely to be linked to a worse prognosis, with the possible exception for SD. If suggested by the patient's history, suspected triggers of CIndU should be assessed for their relevance by challenge tests to diagnose CIndU [17] (Table 7.2). CSU and concomitant CIndU in the same patient can be improved with a similar treatment strategy including antihistamines and omalizumab in refractory cases. A strong body of evidence supports the use of omalizumab in the treatment of patients with CSU as well as difficult-to-treat CIndU [5, 29, 123], although studies that compare the efficacy of omalizumab in patients with CSU vs CIndU vs CSU and CIndU are lacking.

Table 7.1 Comorbid diseases as clinical markers of CSU characteristics and response to treatment

	Higher prevalence and/or risk of comorbidity in CSU patients vs controls?		Marker of progression from acute spontaneous urticaria to CSU?		Longer duration of CSU?		More severe CSU?		A worse response to sgAHs?	
Comorbid disease	Response	Level of evidence[1], [Ref]	Response	Level of evidence[1], [Ref]	Response	Level of evidence[1], [Ref]	Response	Level of evidence[1], [Ref]	Response	Level of evidence[1], [Ref]
Chronic inducible urticaria	+	III [21]	+/−	III–IV [9, 25, 26]	+[2]	III [7–11]	+	III [9]	+[2]	III [9, 24, 27–31]
Mental disorders	+	IIb [1, 32–41]	−	IV	−	III [36, 38, 41, 42]	−[3]	III [33, 36, 41, 42]	ø	ø
Autoimmune thyroid diseases	+[4]	IIb [1, 3, 13, 15, 43–46]	+	III [12, 13]	+/−	III [12, 13, 47–51]	+/−	III [49, 50, 52–54]	−	III [28, 31, 52, 55–59]
Other autoimmune diseases	+[4,5]	IIb [3, 43, 44, 60–69]	ø[7]	ø	ø[6]	ø	ø	ø	ø	ø
Helicobacter pylori	+/−	IIb [70–76]	ø	ø	−	III [47, 77–80]	−/+	III [70, 74, 77, 81]	ø	ø
Parasitic infection	+[14]	III [82–86]	ø	ø	ø	ø	ø	ø	ø	ø
Hepatitis B, hepatitis C or HIV infection	−/+[13]	IIb [1, 61, 87–94]	ø	ø	+/−	III-IV[88]	ø	ø	ø	ø
Fungal hypersensitivity	+/−	III [95–101]	ø	ø	−	III [102]	ø	ø	ø	ø

Allergic diseases	+/−	IIb [1, 11, 21, 26, 43–45, 60, 61, 103–106]	+/−	[25, 26, 107, 108]	−	[8, 47, 109, 110]	−	[21, 109]	−/+	[51, 105, 109]
Malignancy	+/−	IIb [1, 44, 111–114]	ø	ø	ø	ø	ø	ø	ø	ø
Metabolic syndrome	+[8]	IIb [1, 6, 45, 60, 115–119]	−[12]	III [26]	+[9]	III [47, 118, 119]	+/−[10]	III [115, 119, 120]	+/−[11]	III [27, 31, 115, 120]

+: association is shown in all or all but one study
−: association is not shown in all or all but one study
ø: association is unknown (no data)
+/−: inconsistent evidence with most studies supported the association
−/+: inconsistent evidence with most studies reported against the association
[1]Highest level of evidence of supporting study according to the grading system published by the US Agency for Healthcare Policy and Research Classification (www.ahrq.gov) [121, 122]:
Category of evidence
Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least one randomized controlled trial
IIa Evidence from at least one well-designed controlled study without randomization
IIb Evidence from at least one other type of quasi-experimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies, correlated studies, and case studies
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
[2]with the possible exception for symptomatic dermographism
[3]however, presence of mental disorder in CSU was associated with a more pronounced reduction of quality of life
[4]in addition, an association of presence of autoimmune diseases with type IIb autoimmune CSU was recently shown [221, 222]
[5]it is primarily true for systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia, insulin-dependent diabetes mellitus, Sjögren's syndrome, celiac disease, psoriasis and vitiligo
[6]CSU linked to higher SLE activity [223]

(continued)

Table 7.1 (continued)

[7]presence of antinuclear antibodies was not associated with progression from acute urticaria to CSU [12]
[8]in CSU, the risk of metabolic syndrome and its components, hypertension, hyperglycemia/diabetes type II, hyperlipidemia and obesity, is increased. However, in one study, risk of CSU was not increased in patients with type 2 diabetes mellitus, hypertension, or dyslipidemia compared to those without [45]
[9]association with a longer CSU duration was shown for obesity, hypertension and hyperlipidemia
[10]in one study, association between presence of hyperlipidemia and severity of CSU was shown. Another study did not report such association for obesity
[11]no association between obesity and a worse response to AHs was shown
[12]for obesity
[13]in one study, urticaria patients had a higher risk for hepatitis B and C but acute urticaria, inducible urticaria and urticarial vasculitis were not excluded
[14]it is true for protozoa, primarily *Blastocystis hominis*, toxocariasis and fasciolosis seropositivity, *Anisakis simplex* sensitization and strongyloidiasis. These associations are likely to be country-dependent. In some studies, only patients with undefined urticaria were included

Table 7.2 Management of comorbid diseases in CSU patients

Comorbid disease	Most prevalent types/ pathogens	Gender and/or age predisposition	Proposed mechanisms	Personal history, complains and signs of the comorbid disease	Routine diagnostic tests (possible findings)	Extended diagnostic program if indicated by history	Should UV be excluded in the first place?	Treatment of the comorbid disease	CSU remission was shown after treatment of the comorbid disease?
Chronic inducible urticaria	Symptomatic dermographism, DPU	Females	Unknown, might be IgE or IgG autoreactivity	Wheals and/or angioedema due to external stimuli	No	Challenge tests	No	Avoidance of triggers and same treatment strategy as for CSU	Remission is possible because the treatment is the same
Mental disorders	Depression, anxiety	–	–	Specific complains (e.g., depressed mood), past history of a mental disorder	No	Specific questionnaires for mental health evaluation, consultation of a psychiatrist and/or psychologist	No	Psychotropic medications, e.g., doxepin, psychotherapeutic treatments and behavioral interventions	Some psychotropic medications, e.g., doxepin, may be effective in both CSU and a mental disorder
Autoimmune thyroid diseases	Hashimoto's thyroiditis	Adult females	Immune complexes, complement activation, IgE autoantibodies and/or the systemic low-grade inflammation	Complains specific for hyper- or hypothyroidism; can be asymptomatic	No	Antithyroid antibodies, TSH, consultation of an endocrinologist	No	Levothyroxine or antithyroid drugs	Yes, in some patients after treatment of hypo- or hyperthyroidism

(continued)

Table 7.2 (continued)

Comorbid disease	Most prevalent types/ pathogens	Gender and/or age predisposition	Proposed mechanisms	Personal history, complains and signs of the comorbid disease	Routine diagnostic tests (possible findings)	Extended diagnostic program if indicated by history	Should UV be excluded in the first place?	Treatment of the comorbid disease	CSU remission was shown after treatment of the comorbid disease?
Other autoimmune diseases	Vitiligo, pernicious anemia, SLE, insulin-dependent diabetes mellitus, celiac disease	Adult females; children (e.g., celiac disease, type I diabetes)	IgG and IgE-mediated autoreactivity, chronic inflammation, activation of the complement and/or coagulation systems	Complains specific for each autoimmune disease	DBC (leukocytosis), ESR, CRP (increased levels)	ANA, specific autoantibodies, complement, consultation of a rheumatologist	Yes	Immunosuppressive and immunomodulatory therapy, biologics, other specific treatment	CSU may improve due to treatment of comorbid disease
Bacterial infection	*Helicobacter pylori*	–	Direct activation of MCs by HP proteins, molecular mimicry	Can be asymptomatic	No	Testing for HP only after considering other CSU causes	No	Eradication with antibiotics	Yes, but evidence is inconsistent
Other bacterial infection	Focal infections, e.g., dental infection, streptococcal tonsillitis	–	Chronic inflammation, IgE autoreactivity	Specific for each infection	DBC (leukocytosis), ESR, CRP (increased levels)	Search for infection	No	Antibiotic therapy or other treatment if indicated	Yes, some cases are published

Parasitic infection	Protozoa, primarily *Gardia spp.* and *Blastocystis hominis*, and helminths, mostly *Anisakis simplex*, Strongyloides *stercoralis* and *Toxocara canis*	–	Presence of the parasite in the skin, IgE-mediated allergy, Th2 cytokine skewing, eosinophils, and/or activation of the complement and/or coagulation	Residence in or recent travel to a parasite-endemic area, dietary habit, GI symptoms	DBC (unexplained eosinophilia)	Consultation of a parasitologist, serologic testing for parasites, stool for parasites, etc.	No	Antiparasitic treatment or fish free-diet (in case of *Anisakis simplex* hypersensitivity)	Yes, especially in patients with previously diagnosed parasitic infection
Viral infection	Chronic hepatitis B and C, HIV	–	Activation of skin MCs by protein Fv produced during viral hepatitis; hyperbilirubinemia; immune complexes; complement activation	Signs and symptoms and / or past history of viral infection	DBC; ESR, CRP (increased levels)	Anti-HCV, HbsAg, anti-HIV, cryoglobulins	Yes	Antiviral treatment if indicated	No, in most CSU patients with viral hepatitis
Fungal infection	*Candida albicans*, *Trichophyton spp.*	–	Hypersensitivity to fungi antigens	Signs of fungal infection	No	Search for fungal infection, allergy tests to fungi	No	Antifungal treatment or avoidance of allergens	Yes, in a few published reports

(continued)

Table 7.2 (continued)

Comorbid disease	Most prevalent types/ pathogens	Gender and/or age predisposition	Proposed mechanisms	Personal history, complains and signs of the comorbid disease	Routine diagnostic tests (possible findings)	Extended diagnostic program if indicated by history	Should UV be excluded in the first place?	Treatment of the comorbid disease	CSU remission was shown after treatment of the comorbid disease?
Allergic diseases	Asthma, atopic dermatitis, allergic rhinitis and other allergic diseases	Depends on the disease	IgE-mediated hypersensitivity	Symptoms of allergy	DBC (eosino-philia)	Allergy tests, total IgE	No	Avoidance of allergens, antiallergic therapy, allergen-specific immunotherapy	Yes, if CSU is allergic
Malignancy	Solid tumors (more often), hematologic neoplasms	Adults	Immune dysregulation, chronic inflammation, activation of complement and/ or coagulation	Specific signs and symptoms of malignancy	DBC; ESR, CRP (increased levels)	Search for malignancy	Yes	Surgical therapy, chemotherapy and / or radiation therapy	Yes, in most reported cases
Metabolic syndrome	Obesity, dyslipidemia, hyperglyce-mia, hypertension	Adults	Low-grade inflammation	No or specific symptoms	DBC; ESR, CRP (increased levels)	Measurement of blood pressure, BMI, serum levels of glucose and lipids	No	Specific therapy	Unlikely

UV urticarial vasculitis, *DPU* delayed pressure urticaria, *GI* gastrointestinal symptoms, *MCs* mast cells, *DBC* differential blood count, *ESR* the erythrocyte sedimentation rate, *CRP* C-reactive protein, *TSH* thyroid-stimulating hormone, *SLE* systemic lupus erythematosus, *BMI* Body Mass Index, *ANA* antinuclear antibodies, *HP* Helicobacter pylori

7.3 Mental Disorders

Mental disorders are relatively frequent in the general population with 12–49% affected [124], and they may be more prevalent in CSU patients. In several studies, psychiatric comorbidities were found to be present in 5–60% of patients with CSU. The most frequently recorded diagnoses were depression (3–40%) and anxiety (5–30%) [9, 23, 24, 32, 42, 125]. Other mental disorders included posttraumatic stress disorder (3–34%), somatoform disorder (6–17%), adjustment disorder (4%), harmful use of alcohol (3%), bipolar disorder (2%), hypochondria (2%), obsessive-compulsive disorder (2%), alcohol dependency (1%), and multiple substance abuse (1%) [32, 33, 42]. In one study, 17% of CSU patients had a psychiatric disorder in the past [42].

In several population-based studies, undefined chronic urticaria or CSU was associated with a significantly increased risk of mental disorders [1, 34]. Patients with CSU experienced higher levels of stress, somatization, obsessive-compulsive disorder, depression, and/or anxiety than controls [32, 33, 35–41]. For example, in a nationwide study of 14,859 Italian CSU patients, CSU was statistically significantly associated with anxiety, dissociative and somatoform disorders [1]. Furthermore, CSU patients showed higher scores for hysteria, paranoia, psychasthenia, psychopathic deviation, social introversion personality traits [38], posttraumatic stress disorder, [33] and alexithymia [126] as compared to controls. Urticaria was one of the most common conditions in patients with bipolar disorder (9%) [127]. Increased prevalence of urticaria was found among patients with attention-deficit/hyperactivity disorder as compared to the control group [128]. Patients treated for CSU significantly more often visited psychiatrists and psychologists than controls without CSU [129].

The presence of psychiatric comorbidity in patients with CSU, in two studies, was associated with a more pronounced reduction of quality of life, and the severity of psychiatric disease correlated with quality of life impairment [36, 130]. All but one study reported that the duration of CSU and the presence of psychiatric comorbidity are not linked [36, 38, 41, 42]. Furthermore, no correlations were found between comorbid psychiatric diagnoses and CSU severity [33, 36, 41, 42] (Table 7.1).

In summary, psychiatric disorders, primarily depression and anxiety, are important comorbidities of CSU. They are common, and they significantly contribute to the quality of life impairment of CSU. Exploring CSU patients for comorbid psychiatric diseases can help their management and improve quality of life and reduce emotional distress [32, 38]. Strategies for investigating and approaching mental disease in CSU patients include the use of specific questionnaires for evaluating mental health in routine clinical practice and referral to specialists for diagnosing and treating psychiatric diseases.

7.4 Autoimmune Diseases

CSU is autoimmune in some patients [131], and patients with CSU are known to have higher rates of other AIDs. In a systematic review, the prevalence of individual AIDs in CSU was higher as compared to the general population (≥1% vs ≤1%) [4]. Vice versa, the prevalence of urticarial rash in patients with AIDs was >1% in most studies. Furthermore, in several large population-based studies, patients with chronic urticaria were found to be at higher risk for comorbid AIDs than controls [3, 13, 43, 60].

The most prevalent AIDs in CSU are Hashimoto's thyroiditis (HT, ≥5%), pernicious anemia (≥5%), and vitiligo (≥3%)[4, 15, 24]. On the other hand, chronic urticarial rash was found to be most frequent in eosinophilic granulomatosis with polyangiitis (EGPA ≥10%), AITD (>7%), and systemic lupus erythematosus (SLE, >5%)[4, 15, 132]. In CSU, organ-specific autoimmune comorbidities (most prevalent: HT) were seen more often than systemic AIDs (most prevalent: connective tissue diseases, e.g., SLE). AIDs with high and low prevalence in the general population are also common and rare in CSU patients, respectively [4].

AITD in combination with other AIDs occurs in 1–6% of CSU patients. Interestingly, CSU has been described as a part of "autoimmune polyglandular syndrome" (APS). In fact, more than 2% of CSU patients have AITD and vitiligo (APS type 3C, 1–5%) or AITD and pernicious anemia (APS type 3B, 5–6%). Urticarial rash was reportedly seen in 9% of patients with APS type 1, which includes chronic candidiasis and/or chronic hypoparathyroidism and/or Addison's disease. The prevalence of three or more coexistent AIDs and overlap syndromes appears not be increased in CSU patients (15% of CSU patients [4].

Thyroid autoimmunity was described to be linked to the progression of acute spontaneous urticaria toward CSU [12]. In contrast, evidence regarding the association between levels of antithyroid antibodies and CSU duration or severity/activity, gender and age of patients, autologous serum skin test response, or response to treatment is inconsistent or negative [15] (Table 7.1). Autoimmune comorbidities may, however, be important when it comes to the choice of treatment of CSU patients. In a recently published systematic review, of 285 CSU patients treated with thyroid medication in 22 studies, CSU improved in 42% cases. CSU responded to such treatment in hypothyroid, hyperthyroid, and even in some euthyroid patients [15]. Both CSU and comorbid AIDs may benefit from immunosuppressive treatment. For example, all symptoms of CSU and SLE in a five-year-old female improved after therapy with prednisolone and cyclosporine [133]. However, further research is needed because many previous studies were small, uncontrolled and/or had other limitations of design.

In summary, CSU patients are at risk of developing AIDs, and this is especially true for middle-aged female patients with a positive family history for autoimmune disease [4]. AITD, mostly HT, is the most common autoimmune comorbidity in CSU. In CSU patients with elevated IgG antithyroid antibodies and/or risk for AITD, annual reassessment of thyroid function may be warranted [15]. In hypo- and hyperthyroid CSU patients, treatment with levothyroxine or antithyroid drugs,

respectively, can improve CSU. In individual euthyroid patients with difficult-to-treat and long-lasting CSU and presence of antithyroid antibodies, levothyroxine can be regarded as an alternative treatment. Treatment with immunosuppressive drugs and/or biologicals may improve both CSU and comorbid autoimmune disease, e.g., SLE.

7.5 Infection

7.5.1 Bacterial Infection

Chronic infections with various bacteria have been linked to the pathogenesis of CSU including *Helicobacter pylori* (HP), *Staphylococci,* and *Streptococci* [16]. HP is considered responsible for the majority of peptic ulcers, as well as chronic gastritis. The results of studies of the rates of CSU patients with HP infection are controversial. In some studies [70–72], but not in the others [73–75], CSU patients had a higher prevalence of HP infection than controls. A meta-analysis of observational studies involving 965 CSU cases and 1,235 controls suggested that HP infection is significantly, though weakly, associated with an increased risk of CSU [72]. In CSU, the prevalence of HP infection ranged from 10 to 77%, across studies [73, 76, 134–136].

There are studies where HP eradication reduced CSU disease activity [77, 134, 137–139]. On the other hand, many studies did not find that HP eradication leads to CSU improvement [73, 75, 78, 135, 140]. Only three placebo-controlled, double blind trials have been carried out so far [137, 138, 140], two of which linking HP treatment to CSU improvement [137, 138]. In a systematic review of 10 studies, eradication of HP was both quantitatively and statistically associated with remission of CSU [139]. Wedi et al. analyzed pro- and contra-studies and found that the rate of chronic urticaria remission or improvement is nearly doubled when HP is eradicated [16]. In contrast, using the GRADE approach, another review arrived at the conclusion that "evidence that H. pylori eradication leads to improvement of chronic urticaria outcomes is weak and conflicting" [141].

Focal bacterial infections have been reported in 0–50% of CSU patients [25, 136, 142, 143]. These include sinusitis (0.3–32%), dental infection (1–29%), tonsillitis (6–9%), urinary infection (0.5–6%), and lung infection (0–18%) [25, 136, 142–145].

Many reports have linked CSU to dental infection [136, 144, 146–149]. For example, in four cases, CSU cleared or improved after teeth extraction due to periapical abscesses and/or removing caries [146–149]. Of 929 patients with chronic angioedema without wheals, 3% patients had an infection. Appropriate treatment of the infection markedly improved the angioedema in 11 patients with dental granuloma [145]. Of 17 CSU patients with dental or ear-nose-throat infection or yersiniosis, 12 showed remission of their CSU after treatment of the focal infection [136]. Urticaria improved in two cases of sinusitis and in four cases of tooth infection [144]. However, two other studies did not find a significant association between CSU and dental infection [150, 151].

Streptococcus spp. infection occurs as tonsillitis, pharyngitis, cystitis, peritonitis, and rheumatic fever [152]. Levels of antistreptococcal antibodies are reportedly raised in up to 37% of CSU patients [142, 143]. However, in a study by Hellgren and Hersle, no significant difference was found in antistreptolysin antibody titers between patients with chronic urticaria and healthy controls [142]. Evidence for the relevance of streptococcal infection is anecdotal, controlled trials are lacking. Chronic urticaria in some of 16 children in a series by Buckley and Dees went into remission after antibiotic therapy of streptococcal infection [153]. In two patients with CSU and streptococcal tonsillitis, CSU resolved after tonsillectomy. A temporal relationship between CSU exacerbations and tonsillitis was reported [154]. In three out of seven cases with streptococcal infection, improvement of chronic urticaria was seen upon antimicrobial treatment [155]. Bonanni et al. suggested an asymptomatic chronic streptococcal infection in eight of nine CSU patients who benefited from antibiotic treatment [156]. In two patients, antibacterial therapy of urinary tract infection resulted in clearing of chronic urticaria symptoms [25, 157].

Evidence for a link of staphylococcal infection and chronic urticaria is just as weak. Antistaphylolysin antibodies have been detected in 0.3–3% of urticaria patients [143, 158]. Ertam et al. observed statistically higher growth of *Staphylococcus aureus* on cultures prepared from nasal swabs of chronic urticaria patients as compared to the control group [159]. Of 32 chronic urticaria patients with *Staphylococcus aureus* detected in swab specimens from the nasal cavity, 13 patients had complete or partial recovery from urticaria after antimicrobial treatment, whereas the remaining 19 patients (59%) experienced no change of their urticaria [160]. High levels of specific IgE against *Staphylococcus aureus* enterotoxins have been observed in CSU patients [161, 162]. Interestingly, *Staphylococcus* enterotoxin B-IgE levels were strongly correlated with CSU disease activity [161].

In summary, the prevalence and relevance of comorbid bacterial infections in CSU are still ill characterized. Therefore, in CSU, routine screening for HP and other infections is not recommended. In CSU patients with chronic infections with HP, but also *Staphylococcus* or *Streptococcus*, antibiotic therapy can help to reduce CSU symptoms, but should be used only if the infection is properly diagnosed.

7.5.2 Parasitic Infection

In 1895, Duke described two of the first cases of urticaria associated with parasitic infection in Indian soldiers infected by Filaria medinensis [163]. Since then, parasitosis has been reported in up to 75% CSU patients although the prevalence is ≤10% in most studies. Two of three patients with parasitic infection have urticaria including CSU (>10% in most studies) [82]. The most prevalent parasites in CSU reported in the literature are protozoa, mostly *Blastocystis hominis* and *Giardia spp.* [82], whereas helminths are more rarely discovered. For example, CSU was associated with *Enterobius vermicularis* only in 0.1–1.4% of CSU patients [164, 165]. However, in some studies *Toxocara canis* infection was reported in up to 14–29%

of CSU patients [166, 167], and *Anisakis simplex* hypersensitivity had rates of 50–53% [83, 168] compared with 16–20% in the normal population [169].

Anisakis simplex, a nematode, causes IgE-mediated reactions and/or gastrointestinal symptoms, after intake of raw or undercooked fish [169]. CSU patients had significantly higher rates of *Anisakis simplex* sensitization, protozoa infection, and higher risk for *Toxocara canis* seropositivity as compared to healthy controls [170–172]. Patients with undifferentiated urticaria or chronic urticaria more frequently had seropositivity of fasciolosis [166], *Blastocystis hominis,* [173] and Microsporidia [174] infections than controls. Vice versa, patients with strongyloidiasis or *Blastocystis hominis* infection showed increased rates of urticaria as compared to controls [82]. In a cross-sectional Cambodian study including 3,377 participants, urticaria and itching were more frequently reported by patients infected by *Strongyloides stercoralis* [84]. However, Vandenberg and coworkers could not find an association between *Dientamoeba fragilis* infection and urticaria [175].

Peripheral blood eosinophilia is an important sign of both endemic worldwide parasitic infection (e.g., strongyloidiasis, toxocariasis, trichinellosis, hookworm infection) and parasitic infection relevant to certain geographic areas (e.g., filariasis, schistosomiasis). Notably, Giardia and other protozoa generally do not produce eosinophilia, except for *Isospora belli*, *Dientamoeba fragilis*, and *Sarcocystis species* [176]. Some patients have asymptomatic parasitosis, whereas others can have various manifestations including respiratory and gastrointestinal symptoms [177]. For example, rates of elevated ESR and presence of gastrointestinal symptoms, e.g., abdominal pain and vomiting/nausea, were significantly higher in children with CSU associated with parasites, mostly *Blastocystis hominis*, than in those without [164]. In addition, abdominal pain, diarrhea, itching, and chronic urticaria were frequently seen in patients with *Strongyloides stercoralis* infection [84].

Parasites can be regarded as the underlying cause of CSU if the antiparasitic treatment results in the eradication of the parasite and CSU resolution. In a systematic review, 36% of 269 CSU patients experienced improvement of their urticaria after the treatment of their parasitic infection with antiparasitic drugs. No improvement of CSU was reported in five of 21 studies (64% nonresponders) [82]. Fish-free diet was more effective in patients with chronic urticaria and *Anisakis simplex* sensitization as compared to controls [83, 168]. Interestingly, urticaria improved in 97% of 88 patients with previously diagnosed parasitic infection after treatment with antiparasitic drugs [82]. For example, urticaria and abdominal pain mostly resolved in patients with *Strongyloides stercoralis* infection after treatment with ivermectin [84].

In summary, although parasitic infection is not a frequent comorbidity of CSU in many parts of the world, urticaria including CSU is seen in >10% patients with parasitic infection. Protozoa, primarily *Gardia spp*. and *Blastocystis hominis*, and helminths, mostly *Anisakis simplex*, *Strongyloides stercoralis* and *Toxocara canis*, are likely to be the most responsible parasites in urticaria but further research is needed. Parasitic infection is an uncommon underlying cause of CSU in non-endemic countries, and routine screening for parasitic infection in CSU patients is not recommended. However, a history of residence in or recent travel to a

parasite-endemic area (some parasites are endemic worldwide), relevant dietary habits (e.g., consumption of raw fish), concurrent gastrointestinal symptoms (e.g., diarrhea, abdominal pain), and unexplained eosinophilia may be helpful in suggesting a comorbid parasitic infection. These factors should prompt parasite-specific diagnostic tests in CSU patients. If infection is confirmed, specific treatment of parasitosis can improve CSU. A fish free-diet may be effective for the treatment of CSU due to hypersensitivity to *Anisakis simplex*.

7.5.3 Viral Infection

Viral hepatitis, HIV, herpes, and some other infections have been discussed in the context of CSU. Although acute urticaria or acute recurrent urticaria can appear as a prodromal manifestation of acute viral hepatitis A and B [178, 179], the prevalence of CSU in chronic hepatitis B and C infection or vice versa is not increased (Table 7.1) [87]. In a systematic review of 32 studies, less than 5% and 2% of CSU patients had viral hepatitis B and C, respectively [87]. Urticarial rash including CSU occurred only in ≤3% of patients with chronic hepatitis C infection. Moreover, only two out of nine patients showed improvement of their CSU after antiviral treatment of hepatitis C. In a population-based study, urticaria patients were at higher risk of hepatitis B and C than age- and sex-matched controls [61]. However, in this study, acute urticaria, inducible urticaria, and urticarial vasculitis were not excluded. Urticarial vasculitis is known to be related to chronic hepatitis C and mixed cryoglobulinemia and improved in most patients after antiviral therapy [180].

Only a few studies have looked for a link of HIV infection and CSU [1, 181–183]. For example, Supanaranond et al. reported urticaria in 3–6% of HIV-infected patients [182]. Notably, in a population-based study, the risk of CSU was not associated with HIV infection [1]. In two patients with recurrent genital herpes simplex infection, episodes of genital herpes were associated with exacerbation of CSU. CSU improved after treatment with acyclovir [184] or raltegravir, a retroviral integrase inhibitor [185]. Little is known about the prevalence and relevance of other viruses, e.g., norovirus, parvovirus, HHV-6, in CSU [16].

In summary, viral infections including viral hepatitis, HIV and herpes virus, are unlikely to be linked to CSU and the current evidence does not support that these comorbidities are increased in prevalence or relevant in CSU patients. Routine screening for these infections in patients with CSU is not cost-effective and should not be performed unless risk factors or signs and symptoms of these infections are present, or urticarial vasculitis is suspected.

7.5.4 Fungal Infection

Several fungal agents, namely *Candida albicans*, *Trichophyton spp.,* and *Malassezia furfur,* have been discussed as possible comorbidities of CSU. In a retrospective study, 12% (267/2,221) of patients with urticaria including CSU had concomitant

mucocutaneous candidiasis, and this was more than twice as often as compared to control patients [95]. Vice versa, 46% (12/26) of women with recurrent candida infections also had chronic urticaria [186]. However, Ergon and coworkers did not find differences between chronic urticaria patients and controls in intestinal and oral colonization of *Candida spp.* and IgG, IgM, and IgA anti-*Candida* antibodies [96]. Moreover, according to James and Warin, the carriage rate of Candida albicans in the general population is 10–70% [102], which is similar to that in CSU patients.

Five to 36% of patients with chronic urticaria including CSU had positive intradermal tests to *Candida albicans* antigen [97, 102, 187–189]. The rate of over 2+ skin reactions was markedly greater in CSU patients than in controls [97]. Furthermore, CSU patients with positive skin tests to *Candida albicans* had higher rates of positive skin tests to other allergens and positive past and family history of hay fever or asthma [102]. In addition, CSU patients with positive skin tests to *Candida albicans* significantly more often had *Candida albicans* in swab and/or stool tests and exacerbation of their urticaria after challenge tests to *Candida albicans* extract than those with negative skin tests [102]. Increased IgE antibodies to *Candida albicans*, but not to common molds, were detected in 13% of CSU patients [98].

Similar hypersensitivity was demonstrated in CSU patients with fungal infections of the nails, feet, and/or hands after skin tests with *Trichophyton* antigens and passive transfer of patient's serum to a healthy non-hypersensitive subject [99, 100, 190, 191]. 10–29% CSU patients were positive to intradermal testing with *Saccharomyces cerevisiae* antigen [188, 189]. In one study, 61% of CSU patients had a positive response in challenge testing with food yeasts [102].

Candida therapy (nystatin and/or amphotericin B) resolved CSU completely in 8% of skin test positive, but also in 6% of skin test negative patients [102]. In another study, nystatin treatment produced a clinical cure in 55% patients with chronic urticaria, who had immediate skin wheals to *Candida albicans* provocation testing [189]. Gama et al. described four cases of leukorrhea/vulvovaginitis, with improvement of urticaria after the treatment for laboratory-proven candidiasis [155].

In a CSU patient with a positive scratch and intradermal test to *Trichophyton interdigitale* extract [192], both dermatophytosis and CSU promptly relieved after treatment with alcoholic solution of iodine and injections of increasing doses of the diluted fungus extract. In a patient with *Epidermophyton floccosum*-associated dermatophytosis, the dermatophytosis and urticaria healed in 10–14 days after treatment with oral antihistamines and topical clotrimazole [193]. Difficult-to-treat CSU in four Indian patients with tinea infection was successfully resolved with oral antifungal therapy including oral terbinafine, fluconazole, and/or griseofulvin. Clearance of the infection coincided with that of urticaria with no relapse for the next 1–8 weeks [194]. However, in several cases, treatment of proven cases of *Trichophyton* infection did not result in the remission of urticaria [190, 195].

Malassezia furfur infection was found in 65% (82/126) of patients with chronic urticaria, which was significantly more than in normal control subjects. No significant difference was observed between patients treated with AHs or AHs combined

with 2% ketoconazole shampoo by the end of treatment [101]. A low-yeast diet reduced CSU symptoms in some patients [102, 188, 189].

In summary, some CSU patients exhibit hypersensitivity to *Candida albicans, Trichophyton* spp., or Saccharomyces cerevisiae as shown by positive skin tests and/or IgE antibodies against fungal antigens. However, the clinical relevance of cutaneous and mucosal fungal infection in CSU is still unknown, and antifungal treatment yielded controversial effects on CSU symptoms. As of yet, the search for underlying fungal infection as well as diagnostic tests for fungi allergy in CSU patients is not recommended to be performed routinely [5]. In CSU patients allergic to fungi, avoidance of allergens including a low-yeast diet may help to reduce CSU, and in CSU patients with clinically relevant fungal infection, antifungal treatment might improve CSU.

7.6 Allergic Diseases

On average, 10–40% of the world's population suffers from one or more allergic conditions and the prevalence is increasing worldwide [196]. The prevalence of allergic diseases in CSU is 7–59% [43, 60, 103, 125, 197, 198] and appears to be quite similar to that in the general population [198]. In particular, the rates of asthma in CSU patients were 7–27%, 7–14% for atopic dermatitis, 18–59% for allergic rhinitis, and 19% for other allergies [8, 24, 43, 103, 125, 198–200]. A family history of atopic diseases was reported in 29–57% of CSU patients [197, 198, 201].

Some studies and reviews support the notion that CSU more often affects atopic patients or vice versa [60, 199, 202, 203], whereas other studies argue against a link between chronic urticaria and atopic diseases [197, 204]. A population-based retrospective cohort study including 9,332 patients with chronic urticaria reported a significant association of chronic urticaria with asthma and atopic dermatitis in all age groups [43]. Asthma and atopic dermatitis tended to occur before the onset of chronic urticaria. A cross-sectional study including 11,271 patients with chronic urticaria showed that these patients were much more at risk of allergic rhinitis, atopic dermatitis, and asthma as compared to controls [103]. These studies did not differentiate between CSU and CIndU, unlike another nationwide, population-based, epidemiological study, in which patients with CSU had a 4.7 higher likelihood to develop allergic rhinitis, drug or other allergies, or asthma [44]. Urticaria was significantly more common in children with atopic dermatitis than in children without atopic dermatitis although some cases of urticaria were related to food allergy [104]. In contrast, in another population-based study, acute but not chronic urticaria was significantly associated with allergic diseases and parental history of allergy in pediatric patients [26].

Antihistamines and omalizumab can help to manage the symptoms of both, CSU and allergies, in CSU patients with concomitant allergic asthma [205] and probably other allergic diseases. However, no difference was shown in CSU patients with and without comorbid allergy in terms of the duration and activity of CSU and response to treatment (Table 7.1).

In summary, the results of the studies on the prevalence and relevance of allergic conditions in CSU patients are controversial. Further research is needed to evaluate if CSU patients are at increased risk for developing allergic diseases or vice versa. Unlike acute urticaria, type-I-allergy is a rare cause of CSU in patients who present with daily symptoms but may be considered in CSU patients with intermittent symptoms [5]. Atopy can usually be excluded as a cause of urticaria if there is no temporal relationship to a particular trigger, by either ingestion or contact. Therefore, allergy testing should not be routinely performed in CSU patients, and avoidance of substances is not usually necessary, unless allergic urticaria is suspected. Comorbid allergic diseases should be treated in accordance with clinical guidelines. If allergy is a cause of CSU, then avoidance of relevant type-I-allergens clears urticaria symptoms within 1–2 days. AHs are the first-line treatment of CSU and used widely in many allergic diseases. Omalizumab, an anti-IgE monoclonal antibody, has been shown to be effective in treating resistant CSU as well as asthma and can reduce disease activity in patients with atopic dermatitis or allergic rhinitis.

7.7 Malignancy

Malignant diseases have been reported in 0–9% patients with CSU [111, 112, 136, 206–208]. Among them, 85–92% and 8–15% were nonhematologic and hematologic cancers, respectively [111, 208]. Of the former, the most common were cancers of the hepatogastroenterologic system (46%) and lungs and trachea (16%) in one study [111] and breast cancer (18%) in another study [208]. In a population-based study, the most common cancers in CSU patients were those of the thyroid, liver, and prostate [44]. The frequency of CSU in patients with malignancy is unknown.

In a cohort of 6,913 US adults, a personal history of chronic urticaria was associated with an increased risk of lymphoma, leukemia, or myeloma [113]. A nationwide, population-based Italian study showed a higher risk of developing CSU in patients with a history of malignancies [1]. Another population-based study from Korea reported a 1.4 times higher risk for the concurrence of nonhematological neoplasms in CSU patients than in patients without CSU [44]. Furthermore, a retrospective population-based study of 12,720 Taiwanese patients showed an increased risk of cancer, especially hematologic malignant tumor (the greatest for non-Hodgkin lymphoma) in patients with chronic urticaria. This was true even after excluding patients receiving long-term immunosuppressants [111]. The risk was highest among those aged 20 to 39 years, and neoplasms were mostly detected in the first year following diagnosis of chronic urticaria. In contrast, malignancy was diagnosed only in 3% of 1,155 patients with chronic urticaria in a Swedish study and urticaria was not statistically associated with malignancy in general [112]. Vena et al. reported decreased risk of cancer associated with a history of urticaria [114]. Moreover, Karakelides and coworkers observed that patients with chronic urticaria younger than 43 years were unlikely to have associated monoclonal gammopathy of

undetermined significance or malignancy [208]. In a review of case reports, 67% of patients with urticaria and malignancy were ≥35 years [14].

The data from these studies should be analyzed with caution. Two studies from the 1980s defined urticaria as "allergy," so not all of the patients included may have had CSU [113, 114]. Although the Taiwanese and Swedish studies described above involved big cohorts of patients with chronic urticaria, possible confounders, such as smoking or alcohol use, were not investigated [111, 112]. Importantly, some of the patients may have had urticarial vasculitis or Schnitzler syndrome [111–113, 208], which are known to be associated with malignant tumors [180].

In a recent study, virtually all (95%) physicians dealing with urticaria patients worldwide reported that they hold malignancy to be a rare cause of CSU [209]. In 1976, Curth proposed criteria to define a paraneoplastic syndrome, i.e., a strong causal association between dermatosis and tumor [210]. According to these criteria, CSU can be considered to be paraneoplastic if the following two major criteria are met: (1) CSU and malignancy appear at approximately the same time and (2) both conditions follow a parallel course. However, the first criterion is perhaps overly stringent, because tumors are often difficult to detect and the presence of malignancy can be unknown for months or even years. For example, Larenas-Linnemann et al. reviewed 26 cases of urticaria (17 cases of CSU or undefined chronic urticaria) probably causally associated with malignancy [14]. In 68% patients, urticaria appeared 2–8 months before the malignancy was diagnosed. In 75% cases, neoplasms were detected at an early, asymptomatic stage while searching for a cause of urticaria. Carcinomas were found in 68% patients (24% were papillary carcinomas of the thyroid gland) [211], and hematologic neoplasms were reported in 24% cases. On the other hand, Chen et al. observed cancer of the thyroid gland only in 2% among all types of cancer (11/646) in patients with chronic urticaria [111].

In accordance with the second Curth's criterion, resolution of urticaria was reportedly seen in all patients after cure of the tumor (chemotherapy or resection) within days to a few weeks [14]. In some patients, CSU reappeared after relapse of tumor or tapering of specific therapy [212–214]. The main limitations of these reports are publication bias and that spontaneous remission of CSU is common [7]. In a systematic review of 29 studies involving 6,462 patients with chronic urticarial rash [215], 2% (n = 105, urticarial vasculitis in 60 cases) patients had internal diseases considered to be the cause of urticaria. Among those, a paraproteinemia, polycythemia vera, and various malignancies were detected as an underlying cause of chronic urticarial rash only in three, four, and five patients, respectively.

In summary, cancer is considered to be a very rare cause of CSU even though CSU can resolve with cure of cancer [14, 209]. Consequently, the association between malignancy and CSU warrants further evaluation. As of yet, malignancy screening should not be performed in CSU patients, unless indicated by the patient's clinical history, physical exam, and/or initial CSU workup [5].

7.8 Metabolic Syndrome

MS is not a disease *per se* but rather a constellation of signs and symptoms that collectively confer an increased risk for developing heart disease and diabetes mellitus. In fact, MS includes central obesity, dyslipidemia, hyperglycemia, and hypertension. The prevalence of MS in the general population is 7–25% [216]. Early recognition and treatment of MS can improve patients' long-term health and quality of life [217].

In CSU, MS has been recorded in 16–30% patients [6, 115]. Among MS components, obesity was observed in 8–52% cases, hypertension in 18–31%, hyperglycemia/diabetes in 5–34%, hyperlipidemia in 7–42%, and low levels of high-density lipoprotein in 28% [6, 24, 60, 115, 116]. Although Egeberg et al. did not report an increased risk of cardiovascular diseases in patients with chronic urticaria [117], several population-based studies demonstrated significantly higher prevalence of MS and/or its components in patients with chronic urticaria including CSU as compared to controls [1, 6, 60, 116].

In a Israeli study with 11,261 patients with undefined chronic urticaria and 67,216 controls, chronic urticaria was significantly associated with higher body mass index (BMI) and a higher prevalence of MS, obesity, diabetes, hyperlipidemia, hypertension, chronic renal failure, and gout [6]. Importantly, this association remained significant after adjustment for steroid treatment. In a Taiwanese study that included 9,798 adults with chronic urticaria and 9,798 sex- and age-matched controls, chronic urticaria patients had a significantly higher prevalence of prior diagnosis of hyperlipidemia and risk of hyperlipidemia than controls. Interestingly, atopic dermatitis, a negative control, was not associated with prior hyperlipidemia [60].

Using the National Health Insurance of Taiwan database, 2,460 patients with CSU were compared to 9,840 age-, sex-, and index year-matched controls. CSU patients had a 1.4-fold greater risk of developing subsequent hypertension than the non-CSU cohort after adjusting for sex, age, comorbidities, and nonsedating AH use [116]. In an Italian study with 14,859 CSU patients, the risk of developing CSU was significantly higher in obese subjects [1]. Interestingly, the risk of CSU was not increased in patients with type 2 diabetes mellitus, hypertension, or dyslipidemia as compared to those without [45].

Four additional smaller cross-sectional or prospective studies looked at the association between CSU and MS components [47, 115, 118, 120]. Severe and uncontrolled urticaria was significantly comorbid with MS in chronic urticaria patients [115]. Nebiolo and coworkers showed that hypertension is associated with long duration of CSU [47]. Zbiciak-Nylec and coauthors described a statistically significant association between CSU and obesity, higher BMI, greater affected body surface area, and older age at disease onset. CSU patients with higher BMI values had a tendency towards longer disease duration [118]. In contrast, no differences were observed in terms of duration of chronic urticaria between patients with and without MS [115]. Moreover, in another study, obesity was not linked to the severity of chronic urticaria [120].

MS is characterized by a systemic pro-inflammatory and procoagulating state. Increased levels of inflammatory and coagulations markers, e.g., CRP, IL-6, TNF-α, D-dimer, have been detected in subjects with MS [218, 219]. Moreover, CRP predicts the development of arterial hypertension on follow-up in normotensive subjects [220]. CSU, a chronic inflammatory disorder, is also accompanied by raised levels of CRP, ESR, IL-6, TNF-α, fibrinogen, D-dimer, and other inflammatory and coagulation markers [115, 207]. In a retrospective multicenter study involving 1,253 German and Russian CSU patients, higher levels of CRP were associated with higher CSU activity and arterial hypertension [207].

In summary, there is an increasing body of evidence that CSU is associated with MS. Further studies are needed to clarify whether obesity, dyslipidemia, hyperglycemia, and hypertension are relevant to CSU characteristics and pathogenesis and whether evaluation of MS should be included in routine diagnostic tests for CSU. Components of MS are considered to be major, modifiable risk factors for atherosclerosis, cardiovascular diseases, and diabetes. Therefore, among the higher risk group of patients with CSU, measurement of blood pressure and BMI, and/or a serum examination for hyperlipidemia and glucose should be performed. With prompt detection and appropriate management, CSU patients' quality of life may be improved and subsequent cardiovascular risks may be reduced.

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Inducible Urticarias

8

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8.1 Introduction

Chronic inducible urticaria (CINDU) is a group of diseases that are characterized by the appearance of itchy wheals, angioedema or both, upon exposure to a specific triggering stimulus. Depending on the type of stimulus, CINDU can be classified as physical urticaria (symptomatic dermographism, cold urticaria, heat urticaria, delayed pressure urticaria, solar urticaria, and vibratory angioedema) or nonphysical urticaria (cholinergic urticaria, contact and aquagenic urticaria; Table 8.1) [1]. In most cases, CINDU is a very chronic disease lasting for many years. Overall, CINDU is common, but the prevalence of the individual physical and nonphysical urticarias is very different, from very common (i.e. symptomatic dermographism) to extremely rare (i.e. aquagenic urticaria). Most patients suffer from one CINDU, but some may have two or more CINDUs, and many patients with chronic spontaneous urticaria (CSU) have been reported to also have at least one concomitant CINDU. The diagnosis of CINDU is based on the patient history and a positive provocation test to the offending trigger. In all patients with a history suggestive of CINDU, respective provocation testing should, if possible, be performed to confirm the diagnosis. Many patients with CINDU suffer severely from the disease, and the correct diagnosis is required to inform the patient about the nature of the disease and to provide an optimal treatment.

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