

Original Article

The Diagnostic Workup in Chronic Spontaneous Urticaria—What to Test and Why

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What is already known about this topic? The guideline recommends limited tests (differential blood count, erythrocyte sedimentation rate, and/or C-reactive protein) in routine diagnostic of patients with chronic spontaneous urticaria (CSU) and an extended diagnostic program based on patient history.

What does this article add to our knowledge? We formulate simple questions that should be asked at the initial consultation of patients with CSU. Answers to these questions can lead to the identification of patients in whom further investigations should be performed.

How does this study impact current management guidelines? Our recommendations can help to prevent unnecessary and potentially expensive testing and can increase diagnostic accuracy and treatment effectiveness.

BACKGROUND: In chronic spontaneous urticaria (CSU), the guidelines recommend very limited diagnostic procedures during the routine workup, although additional investigations might be indicated in some patients with CSU. For physicians treating patients with CSU, it is often difficult to decide which diagnostic tests are useful.

OBJECTIVE: To provide recommendations on what diagnostic tests should be performed on which patients with CSU.

METHODS: We performed an extensive literature search on the respective topics and identified relevant questions that should prompt diagnostic procedures based on the published evidence and expert consensus among all authors.

RESULTS: We provide questions, diagnostic testing, where appropriate, and recommendation that should be included when assessing the history of a patient with CSU, to explore and rule out differential diagnoses, to assess patients for underlying causes and modifying conditions, to explore patients for comorbid diseases and consequences of having CSU, and to assess patients for CSU components that

can help to predict their disease course and response to treatment.

CONCLUSIONS: Here, we provide physicians treating patients with CSU with information about which clues should lead to which tests and why. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

Key words: Angioedema; Autoimmunity; Autoinflammatory disease; Hives; Urticaria; Urticaria vasculitis; Wheals

THE AIMS AND SCOPE OF DIAGNOSTIC TESTING IN CHRONIC SPONTANEOUS URTICARIA

Chronic spontaneous urticaria (CSU) is defined by the occurrence of wheals, angioedema, or both for longer than 6 weeks. Optimal diagnostic testing in CSU remains in question. Often, too many tests are performed, which many offer little to no diagnostic or predictive value, whereas, alternatively, useful tests are not performed or are not available. The consequences

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Abbreviations used

ACE- Angiotensin-converting enzyme
 ANA- Antinuclear antibody
 ASST- Autologous serum skin test
 BHRA- Basophil histamine release assay
 CBC- Complete blood count
 CIndU- Chronic inducible urticaria
 CRP- C-reactive protein
 CSU- Chronic spontaneous urticaria
 ESR- Erythrocyte sedimentation rate
 HP- Helicobacter pylori
 MC- Mast cells
 NSAIDs- Nonsteroidal anti-inflammatory drugs
 QoL- Quality of life
 TPO- Thyroid peroxidase
 UV- Urticarial vasculitis

include frustration for patients and physicians, delays in treatment, which can lead to suboptimal outcomes, and unnecessary costs.

CSU is a heterogeneous, disabling, and persistent disease with multiple comorbidities and consequences. In these patients, diagnostic tests are performed for various reasons: (1) to confirm the diagnosis and rule out differential diagnoses, (2) to look for underlying causes, (3) to identify relevant conditions that modify disease activity, (4) to identify comorbidities, (5) to determine consequences of the signs and symptoms of CSU, (6) to determine components predicting disease course and/or response to treatment, and (7) to monitor disease course, its activity, impact, and control (Figure 1). To complete the aforementioned, a thorough medical history is crucial in guiding physicians on the selection of adequate and relevant tests. For some of the domains, a symptom-oriented physical examination is necessary. Here, we provide recommendations for assessing the aforementioned domains to guide physicians.

METHODS

A multidisciplinary group of experts in the fields of urticaria, allergology, and dermatologic autoimmune diseases met in 2019 to discuss useful diagnostic measures for CSU based on their clinical experience and published literature. After that meeting, the group was divided into teams where each performed an extensive literature search on the respective topics “differential diagnosis,” “underlying causes,” “conditions that modify disease activity,” “comorbidities,” and “predictors of course of disease and its severity.” All PubMed listed publications until December 2020 were thoroughly reviewed and considered. Finally, each team elaborated relevant questions for daily clinical practice that should prompt diagnostic procedures based on the published evidence and expert consensus among all authors.

RESULTS

Confirming CSU and exploring differential diagnoses

Confirming the diagnosis of CSU is the most important aim of the diagnostic workup. In most cases, this diagnosis is easily established by the history and the presence of CSU-defining clinical signs and symptoms, that is, spontaneously recurring pruritic wheals, angioedema, or both for longer than 6 weeks. Verification of the latter may require reviewing photo documentation provided by the patient, as both wheals and

What to do in every CSU patient			
Questions	Physical examination*	Basic tests**	UCT
* Including review of patient photo documentation ** Differential blood count, CRP/Erythrocyte sedimentation rate, IgG-anti-TPO, total IgE			
C onfirm	Rule out differential diagnoses		
C ause	Look for indicators of CSU ^{aiT1} , CSU ^{aiTIIb}		
C ofactors	Identify potential triggers, aggravators		
C omorbidities	e.g. check for CIndU, autoimmunity, mental health		
C onsequences	e.g. identify problems with sleep, distress, sexual health, work and social performance		
C omponents	Assess potential biomarkers or predictors of treatment response		
C ourse	Monitor CSU activity, impact and control		

FIGURE 1. The 7 Cs in CSU diagnostic. *CIndU*, Chronic inducible urticaria; *CRP*, C-reactive protein; *CSU*, chronic spontaneous urticaria; *CSU^{aiT1}*, CSU due to autoimmunity type I; *CSU^{aiTIIb}*, CSU due to autoimmunity type IIb; *ESR*, erythrocyte sedimentation rate; *TPO*, thyroid peroxidase.

angioedema are transient and short-lived and may not be present during the physical examination. However, there are a number of diagnoses that need to be excluded, especially in patients who present with unusual symptoms or with additional signs and symptoms other than itchy wheals or angioedema and who do not respond to standard treatments of CSU. Depending on the clinical phenotype, wheals, angioedema, or both, differential diagnoses should be explored based on patient symptomatology (ie, those who only or predominantly develop chronic recurrent wheals and those who primarily or exclusively develop angioedema; Table I).¹

In patients with recurrent wheals, urticarial vasculitis (UV) and urticarial autoinflammatory diseases are rare but important to consider.^{2,3} To exclude both, physicians should inquire about the duration and resolution of individual wheals and the coexistence of additional signs and symptoms other than itchy wheals or angioedema such as musculoskeletal pain or episodes of fever. Prolonged duration of >24 hours and slow resolution of individual wheals are suggestive of UV, and additional signs of systemic inflammation can point toward autoinflammatory disease or other autoimmune disorders. If UV or an autoinflammatory disease is suspected, diagnostic tests should include a skin biopsy to look for vascular destruction or neutrophilic infiltrates. As standardized histopathologic criteria for UV are not yet established, it may be difficult to distinguish UV from CSU.⁴ To rule out autoinflammatory conditions or UV with systemic involvement, basic laboratory tests such as the inflammatory markers C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) and/or complete blood count (CBC) with differential are essential⁵ to detect signs of systemic inflammation, although these results can be seen in CSU and can also be influenced by other comorbidities.

TABLE I. Differential diagnoses in patients with CSU

Condition/issue to be considered	Questions and aspects of the physical examination that should lead to further investigations	Diagnostic tests that should be done if clues are obtained from history and physical examination
In patients with wheals only		
Urticarial vasculitis*	• Do you have long-lasting wheals (ie, >24 h)? • Do your wheals leave hyperpigmented bruises?	Skin biopsy, C3, C4, C1q
Schnitzler syndrome	• Do you have extracutaneous symptoms (eg, fever, musculoskeletal pain, malaise) • Are your wheals not itchy?	Skin biopsy, serum immune fixation (monoclonal IgM/IgG); CRP, serum amyloid A, S100 A8/9 or A12
Cryopyrin-associated periodic syndrome	• Do you have the symptoms since childhood? • Do you have extracutaneous symptoms (eg, fever, musculoskeletal pain, malaise) • Are your wheals not itchy? • Do your symptoms exacerbate in cold temperature?	Skin biopsy, CRP, serum amyloid A, S100 A8/9 or A12, mutation analysis in the nod-like receptor protein 3 gene
Still's disease (systemic juvenile idiopathic arthritis and adult-onset Still's disease)	• Do you have extracutaneous symptoms (eg, fever, musculoskeletal pain, malaise) • Skin inspection: maculopapular salmon-colored or urticarial rash? • Physical examination: lymphadenopathy, hepatosplenomegaly?	Skin biopsy, CRP, serum amyloid A, S100 A8/9 or A12, ferritin, liver enzymes
Chronic inducible urticaria*	• Can you make your wheals appear?	Provocation testing with respective trigger (ie, cold, friction, exercise)
In patients with angioedema only		
ACE-inhibitor—induced angioedema	• Are you taking blood pressure medication?	Stop ACE inhibitor intake
Hereditary angioedema	• Does or did anyone in the family have similar symptoms? • Did you ever have abdominal pain attacks?	C4, C1-INH protein and function
Acquired angioedema		C4, C1-INH protein and function, C1q and C1-INH antibodies

ACE, Angiotensin-converting-enzyme; C1-INH, complement component 1-inhibitor; C3/4/1q, complement component 3/4/1q; CRP, C-reactive protein; CSU, chronic spontaneous urticaria.

*Angioedema can also occur.

Several other conditions have to be considered in patients with recurrent wheals. Some are rare entities such as Wells syndrome and hypereosinophilic syndromes.³ Although these patients may also present with urticarial lesions, the primary skin lesions are different, ranging from permanent maculopapular to long-lasting plaque-like lesions. In pruritic urticarial papules and plaques of pregnancy (also known as polymorphic eruption in pregnancy), patients have coexistent wheals and plaques and are pregnant. Premonitory bullous pemphigoid without evidence of vesicles or bullae should be considered in the elderly and requires a skin biopsy to confirm.⁶

In patients presenting with recurrent angioedema without wheals, bradykinin-mediated disorders such as angiotensin-converting enzyme (ACE) inhibitor—induced angioedema, hereditary angioedema, and angioedema due to acquired C1 inhibitor deficiency have to be considered.⁷ Here, the physician should closely review the use of concomitant medication (especially intake of ACE inhibitor), lack of response to antihistamines or corticosteroids, family history, age at onset of symptoms, duration of angioedema attacks, presence of abdominal angioedema episodes, and presence of prodromal symptoms. In all patients with recurrent angioedema in whom a hereditary angioedema or an acquired C1 inhibitor deficiency cannot be ruled out, laboratory assessment should include complement C4

levels and C1 inhibitor concentration and function, to exclude or confirm hereditary angioedema due to C1 inhibitor deficiency.

Recommendation. A thorough medical history should be included in the patient assessment. CSU should be confirmed in all patients through a differential diagnosis that includes blood testing for CRP and/or ESR and CBC with differential. Further testing should be based on aspects detailed in [Table I](#).

Determining the underlying cause of CSU

Determining the underlying cause of CSU remains elusive and challenging for physicians: many physicians are misinformed or unaware of the actual causes of CSU and appropriate testing is not always available. Furthermore, patients are often driven by the idea that testing can identify a specific cause and can be cured, which is not possible in the vast majority of cases. All patients with CSU, independent of the cause, generally receive the same treatments that are limited in number, following the same therapeutic algorithm, although many treatments that target individual causes of CSU are under development. Although the search for underlying causes is a secondary aim of the management of patients with CSU, testing for underlying causes should not delay treatment.

TABLE II. Conditions that can modify disease activity

Condition/issue to be considered	Questions and aspects of the physical examination that should lead to further investigations	Diagnostic tests that can be done if clues are obtained from history and physical examination
Food intolerance	Do you have increased disease activity in association to foods?	Pseudoallergen-low diet
Drug intolerance	Do you have increased disease activity in association with NSAIDs?	Avoiding the intake of NSAIDs
Stress	Do you have increased disease activity in association with stress, anxiety, depression, or sleep impairment?	HADS, referral to psychologist or psychiatrist
Chronic infections	- Do you have any chronic infection (eg, tonsillitis, sinusitis, dental infection, urinary tract infection)? - Do you have recurrent gastrointestinal problems?	ASL titer, referral to GP or respective specialist

ASL, Antistreptolysin titer; GP, general practitioner; HADS, Hospital Anxiety and Depression Scale; NSAIDs, nonsteroidal anti-inflammatory drugs.

The pathogenesis of CSU is not yet fully understood; yet we know that the signs and symptoms are caused by the activation of skin mast cells (MC) and the subsequent release of mediators including histamine.⁸ Recent evidence indicates that there are 3 subgroups of CSU: autoimmunity type I (CSU^{aiTI} or “autoallergic CSU”), autoimmunity type IIb (CSU^{aiIIb}), and CSU due to unknown cause (CSU^{uc}).^{9–15} In some cases, features of type I and type IIb autoimmunity may both be present.¹⁶ In most patients with CSU, CSU^{aiTI}, with IgE autoantibodies to autoallergens, is thought to be the underlying pathomechanism.¹⁷ In CSU^{aiIIb}, IgG or IgM autoantibodies that target activating MC receptors induce MC activation and degranulation. In CSU^{uc}, other, as of yet unknown, mechanisms are relevant for the degranulation of skin MC. In addition, there are modulating factors such as infections, drugs, or stress that can alter the sensitivity of skin MC when responding to degranulators and can thus be responsible for higher disease activity and/or disease exacerbation. Notably, these modulating factors and the conditions they are linked to are not the cause of CSU and will be discussed.

Disease course and response to treatment differ between patients with CSU^{aiTI} and those with CSU^{aiIIb}. Although there is currently no direct therapeutic consequence based on the exact CSU type (type I or type IIb autoimmunity) given currently approved treatments, patients may benefit, nevertheless, from a correct classification. First, patients desire knowledge about their disease. In addition, information about the possible underlying cause can prevent unnecessary and possibly expensive testing. There is some evidence that treatment response differs depending on whether type I or type IIb autoimmunity is present (see below). It is therefore advisable to assess patients with CSU for CSU^{aiTI} and CSU^{aiIIb}. Differentiating factors include time since the onset of disease (longer in CSU^{aiIIb})^{1,2} and concomitant autoimmune diseases (more common in CSU^{aiIIb}).^{13,15,18–20} Also, results of basic CSU tests (ie, CBC with differential, CRP) can differentiate between type I versus type IIb autoimmune CSU, with CRP more often elevated and eosinophil and basophil levels more often reduced in the latter than the former.²¹ More advanced testing including total IgE, antinuclear antibodies (ANAs), and IgG antithyroid peroxidase (TPO) may bring even more clarity, but is only recommended for specialists. Patients with CSU^{aiTI} are more likely to have low or very low total IgE, positive ANAs, and anti-TPO IgG.^{14,15,17,22–24} In fact, elevated IgG-anti-TPO and low total IgE, in combination, is currently the best surrogate marker for CSU^{aiIIb}.¹⁵

The development of tests for type I and IIb autoimmune CSU is an urgent unmet need. Currently, there are no tests that definitively assess CSU^{aiTI}. The ones for CSU^{aiIIb}, that is, the autologous serum skin test (ASST), immunoassays for MC-activating autoantibodies, and basophil testing, are only available at very specialized centers, such as Urticaria Centers of Reference and Excellence.²⁵ CSU^{aiIIb} is likely if patients are positive in either the ASST or basophil testing (basophil activation test or basophil histamine release assay [BHRA]) or if IgG autoantibodies directed against IgE or FcεRI can be detected.^{15,26–28} If IgE antibodies against self (eg, against TPO, interleukin 24, or double-stranded DNA) can be detected, type I autoimmunity is suspected.^{13,14,29,30} Currently, only the basophil test is commercially available.

Recommendation. Physicians should explore patients with CSU for underlying causes by asking relevant questions and by the use of more specific tests, where indicated and available. Specialists should measure total IgE and IgG anti-TPO and, if available, use basophil testing to assess patients with CSU for type I and type IIb autoimmunity.¹⁵

The search for relevant conditions that modify disease activity

Knowledge of relevant comorbid conditions can aid in understanding disease course, its impact, and may assist in mitigating effects. Food, drugs, stress, and infections, for instance, have signals that can trigger CSU exacerbations that can then modulate MC activation and contribute to increased CSU disease activity.

Food intolerance has been repeatedly linked to CSU disease activity.^{31,32} In contrast, IgE-mediated food allergy is rarely the cause of CSU or a relevant modifier of CSU disease activity.⁵ Although several studies have found that patients with CSU can benefit from pseudoallergen- and histamine-low diets,^{32–38} the response rates greatly differ across published works and the evidence level is low, because of the lack of well-designed double-blind, placebo-controlled studies.³⁹ Accordingly, pseudoallergen- and histamine-low diets are still controversial.⁵ To avoid side effects or safety risks, strict diets should only be kept for a limited period of time (3–4 weeks are usually recommended),³² and foods should be added back to the diet as much as possible to avoid food aversion disorders.

Physicians should inquire about exacerbations associated with food and pseudoallergen-low diets (Table II). Notably, not all

TABLE III. Comorbidities

Condition/issue to be considered	Questions and aspects of the physical examination that should lead to further investigations	Diagnostic tests that should be done if clues are obtained from history and physical examination
Hashimoto's thyroiditis	• Adult female with positive family history for autoimmune disease? • Signs or symptoms suggestive of hyper- or hypothyroidism	TSH, fT4, if indicated IgG anti-TPO
Mental disorders	• Do you feel depressed? • Do you feel overly anxious?	HADS, CU-Q2oL, if indicated referral to specialist
Chronic inducible urticaria	• In addition to spontaneous whealing, can you also make your wheals appear?	Provocation tests for CIndU

CIndU, Chronic inducible urticaria; CU-Q2oL, Chronic Urticaria Quality-of-Life Questionnaire; fT4, unbound thyroxine; HADS, Hospital Anxiety and Depression Scale; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

patients with CSU with relevant food intolerance experience food-induced disease exacerbation, nor are they aware of the link between eating certain food and worsening of CSU. Ultimately, diagnostic diets should not delay effective treatment.⁵

Various medications can contribute to MC activation, via IgE- and non-IgE-mediated pathways and are relevant triggers of disease exacerbation in approximately one-third of patients with CSU.⁴⁰ Neuropeptides and eosinophil products have been reported to activate MC via the Mas-related G-protein-coupled receptor X2^{41,42} though nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common drugs to trigger CSU exacerbation, with up to 28% of patients affected.⁴⁰ The exact mechanisms are not yet entirely understood.⁴³ IgE-mediated activation of MC in this context is rare. Physicians should inquire about NSAID intake, particularly on demand use, because patients often do not report NSAIDs because these medications are over-the-counter (OTC) drugs (Table II). Provocation testing is usually not required but may be considered in cases in which urticaria only occurs after the intake of a specific drug.⁴⁴ Avoiding the use of NSAIDs (or other potentially relevant drugs) can limit the burden of disease in some patients.

Stress can exacerbate CSU. Although our understanding of the complex, multidirectional cross-talk between neurons and MC in the skin has increased in recent years, the clinical relevance still needs further investigation to be better characterized. Assessment of the role of stress as a triggering or exacerbating factor in CSU is difficult because the relationship between CSU and stress may be bidirectional. Moreover, the retrospective assessment bears the risk of recall bias. Yet, up to one-third of patients with CSU see stress as an aggravating factor of their disease.⁴⁵ Patients with CSU reported stress-induced exacerbation more frequently than patients with chronic inducible urticaria (CIndU).⁴⁵ Those with CSU show exaggerated neurophysiological responses when exposed to a stressor.⁴⁶ Patient who do not understand the cause of CSU generally have higher levels of stress.^{47,48} Further studies are needed to elucidate the prevalence of stress-induced CSU exacerbation and the underlying mechanisms as well as the value of stress-targeted therapeutic interventions. We recommend inquiring about the impact of stress and encourage stress reduction that can be helpful (Table II).

Acute viral and chronic bacterial infections can exacerbate CSU and modify disease activity, respectively. Evidence suggests that chronic viral infections, such as hepatitis B or C, do not modulate CSU activity⁴⁹; thus, a routine search for chronic viral infections is not recommended. As for chronic bacterial

infections, there are many studies on *Helicobacter pylori* (HP) with heterogeneous, and in part contradicting, results. The incidence of HP infection in patients with CSU reportedly ranges from 26% to 84%^{50,51} and was similar,⁵² higher,^{53,54} or even lower⁵⁵ as compared with healthy controls. The effect of HP eradication on the course of CSU is also controversial.⁵⁶⁻⁵⁹ Physicians should inquire about the signs and symptoms of HP infection and perform follow-up diagnostics as needed.

Some patients with a relevant parasitic infection do not exhibit corresponding signs and symptoms. The reported prevalence of parasite infection varies and ranges from 0% to 76% with very high efficacy of antiparasitic therapy for CSU symptoms.⁶⁰ Given that parasite infections are common in some and rare in other parts of the world, physicians should inquire about patients' travel history and the presence of symptoms. Follow-up diagnostic tests should be completed as indicated. The role of fungal infections in CSU is ill defined, and their prevalence and relevance needs to be better understood before recommendations can be made.^{61,62}

Recommendation. No routine testing for conditions that modify disease activity should be performed. Further diagnostic tests listed in Table II should be considered based on the answers to the respective questions given in Table II.

The search for comorbidities and consequences

Assessment of CSU comorbidities and disease consequences are important parts of the diagnostic workup. Most can be explored using targeted questions and the majority are treatable. In the following, we will discuss the common comorbidities, CIndUs, allergies, and autoimmune diseases as well as mental disorders such as depression and anxiety.

CIndU is a very common comorbidity in patients with CSU⁶³⁻⁷¹ with up to 25% of patients with chronic urticaria presenting with both CSU and CIndU.⁷² Importantly, many patients with comorbid CIndU are unaware of specific triggers that can induce disease signs and symptoms. Patients with CSU with CIndU often have higher disease activity, require longer treatment, and need higher doses of antihistamines compared with those without CIndU.⁶⁴ Among patients with antihistamine-refractory CSU, there is a high incidence of concomitant CIndU,^{68,73} which is a marker for poor overall treatment response.⁷⁴ Knowledge of the relevant triggers and their thresholds can help patients avoid or mitigate the development of the signs and symptoms of comorbid CIndU.

TABLE IV. Laboratory tests and CSU features that are linked to long disease, high disease activity and/or response to treatment

Parameter	Measurement	References
Laboratory tests and CSU features linked to long disease duration		
Elevated IgG anti-TPO		111,112
High CSU severity/activity		111,113
Parameters or biomarkers linked to higher CSU activity		
Elevated prothrombin fragment 1+2		114-117
Elevated D-dimer		116,117
Elevated CRP		11,22,118,119
Elevated mean platelet volume		120-122
Elevated IL-6		123-126
CSU parameters or biomarkers linked to poor response to treatment with sgAHs		
Presence of concomitant CIndU		64,73
ASST positivity		73
High D-dimer		11,127,128
High UAS		73,129-131
High CRP		22,73
Previous corticosteroid treatment		130,131
Low blood basophil and eosinophil counts		21,73
CSU parameters or biomarkers linked to poor response to omalizumab treatment		
Low total IgE		29,132-136
Positive BHRA		137
History of previous immunosuppressive treatment		134,138-140
Low basophil FcεRI expression		132,141
CSU parameters or biomarkers linked to good response to cyclosporine treatment		
Low total IgE		142,143
Positive BHRA		144-146

ASST, Autologous serum skin test; BHRA, basophil histamine release assay; CIndU, chronic inducible urticaria; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; sgAH, second-generation antihistamine; TPO, thyroid peroxidase; UAS, urticaria activity score.

Physicians should inquire to determine if wheals emerge by scratching or by exposing their skin to the cold or sunlight. If yes, suspected triggers of CIndU should be assessed for their relevance by provocation testing⁷⁵ (Table III).

Autoimmunity is the underlying pathomechanism in most patients with CSU,¹⁷ and the overall prevalence of other autoimmune diseases is higher compared with healthy controls.^{53,58,76-78} The most highly prevalent autoimmune disease ($\geq 5\%$) and with clinical impact on CSU is Hashimoto's thyroiditis.^{79,80} The subgroup of patients with CSU with the highest occurrence of Hashimoto's thyroiditis is middle-aged females with a positive family history for autoimmune disease.⁷⁹ Those with CSU^{aiTTIb} exhibit an increased risk of developing autoimmune comorbidities. Thus, we recommend assessing all adult patients with CSU with comorbid autoimmunity, especially Hashimoto's thyroiditis and vitiligo, using targeted questions and measuring IgG-anti-TPO with annual reassessment of thyroid function in positive asymptomatic cases^{81,82} (Table III).

Allergic diseases such as allergic rhinoconjunctivitis, asthma, and atopic dermatitis occur in 7% to 59% of patients with CSU,⁸³⁻⁸⁸ that is, at rates that are comparable with those in the

general population, with up to 40% of the world population reported to have ≥ 1 allergic condition.⁸⁹ Although patients with CSU^{aiTTI} have a higher risk for developing allergic diseases,^{87,90} type I allergies to environmental allergens are an exceedingly rare cause for CSU. In accordance with the current guidelines on the management of patients with CSU, allergy testing for inhalants and/or foods or elimination diets is *not* recommended in patients with CSU.⁵ Nevertheless, existing comorbid allergies should be treated in accordance with the respective guidelines.

Between 5% and 60% of patients with CSU exhibit psychiatric comorbidities,^{64,66,68,88,91-93} and a recent meta-analysis found sleep-wake disorders, anxiety, and mood disorders to be the most prevalent.⁹⁴ Although mental disorders are frequent in the general population (12%-49%),⁹⁵ there are data suggesting that CSU is associated with a significantly increased risk of psychiatric conditions,^{96,97} especially depression and anxiety,^{91,93,98-104} which contribute to decreased patient quality of life (QoL). In patients with CSU, QoL impairment is associated with psychiatric comorbidities and is correlated with the severity of the psychiatric disease.^{93,100} Mental disorders, in patients with CSU, are held to be the consequence of urticaria, with recent studies showing that every year of CSU duration adds to the risk of developing depression and anxiety.¹⁰⁵ Given the high reported prevalence of sleep impairment, anxiety, and depression in patients with CSU, the clinical history should include questions regarding these aspects. When indicated, available screening tools such as Hospital Anxiety and Depression Scale, Beck Depression Inventory, Generalized Anxiety Disorder-7, or Patient Health Questionnaire-9 may be used to identify patients who may benefit from psychiatric or psychology care (Table III).

Data are conflicting about the association of CSU and malignancies. Although some studies report a correlation of CSU with hematologic or nonhematologic cancers,^{90,97,106,107} others show no association or even a decreased incidence.^{108,109} Recently, in a worldwide survey among urticaria specialists, the vast majority of treating physicians stated that malignancies were a very rare cause of CSU.¹¹⁰

Routine screening for malignancies should not be performed in patients with CSU.

Overall, for comorbidities and consequences, relevant findings from the patient's medical history, physical examination, or basic testing should prompt further investigations, that is, screening for specific diseases using questionnaires, provocation tests, laboratory analyses, or referral to a specialist.

Recommendation. No routine testing should be performed for possible comorbidities and consequences. The criteria for patients with CSU that should receive further tests are listed in Table III.

The assessment of CSU components associated with longer disease duration, higher disease activity, and response to treatment

To date, there are no definite predictors of disease duration, activity, or response to treatment. However, there is published evidence that certain features in patients with CSU are associated with these aspects. In Table IV, we summarize the predicting components of CSU and the respective required measurements. For example, elevated IgG anti-TPO and high CSU activity are linked to longer disease duration, whereas elevated prothrombin fragment 1+2, D-dimer, CRP, mean platelet volume, and IL-6

can point to higher disease duration. Furthermore, some parameters are associated with poor response to treatment with antihistamines (presence of concomitant CIndU, previous corticosteroid treatment, high CRP, high D-dimer, high disease activity, and low blood basophil and eosinophil counts) and omalizumab (low total IgE, positive BHRA, history of previous immunosuppressive treatment, and low basophil FcεRI expression) and good response to cyclosporine (low total IgE and positive BHRA).¹⁴⁷ Targeted questions on these components and respective assessments can possibly help in counseling patients on the severity and expected duration of their disease and on what to expect from treatment (Table IV).

Recommendation. CSU activity and concomitant CIndU should be evaluated in all patients with CSU, and CRP and CBC with differential (giving an estimate for blood basophil and eosinophil counts) should be performed as recommended by international guidelines.⁵ In addition, D-dimer and total IgE are recommended to be tested to help in counseling the patient in respect to disease duration and treatment response.

DISCUSSION

Here we provide a comprehensive set of questions that should be asked during the initial consultation of patients with CSU as well as recommendations. Based on the answers, a decision for or against further diagnostic tests can then be made by the treating physician. This is important, as chronic urticaria is a common disease with an estimated point prevalence of 0.7%¹⁴⁸ yet only in certain patients further tests will have diagnostic or predictive value. Asking the appropriate questions, therefore, will prevent unnecessary and potentially expensive testing and increases diagnostic accuracy and treatment effectiveness.

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