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

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Introduction

- Chronic spontaneous urticaria (CSU) is defined by the occurrence of wheals, angioedema, or both for longer than 6 weeks
- It is a common disease with an estimated point prevalence of 0.7%
- Current guidelines recommend very limited diagnostic procedures during initial workup, and it's often difficult to decide which diagnostic tests are useful

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.

Methods

- A multidisciplinary group of experts met in 2019 to discuss useful diagnostic measures for CSU based on their clinical experience and published literature
- The group was divided into teams where each performed an extensive literature search on the respective topics of "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 reviewed and considered
- 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

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.

- Confirming the diagnosis of CSU is the most important aim of the diagnostic workup
- 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 remains elusive and challenging for physicians
- The pathogenesis of CSU is not yet fully understood – recent evidence indicates that there are 3 subgroups of CSU
- **Autoimmunity type I (CSU^{aiTI})** – IgE autoantibodies to auto-allergens is thought to be underlying pathomechanism
- **Autoimmunity type IIB (CSU^{aiTIIb})** – IgG or IgM autoantibodies that target activating MC receptors induce MC activation and degranulation
- **CSU due to unknown cause (CSU^{uc})**

- Although there is no direct therapeutic consequence based on the exact CSU type, patients may benefit from a correct classification
- Differentiating factors include time since onset of disease (longer in CSU^{aiTIIb}), and concomitant autoimmune disease (more common in CSU^{aiTIIb})
- CSU^{aiTIIb} is also associated with elevated CRP, eosinophil, and basophil levels
- CSU^{aiTIIb} more likely to have low total IgE, positive ANAs, and anti-TPO IgG
- Physicians should explore patients with CSU for underlying causes by asking relevant questions and by use of mores specific tests where indicated and available

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.

- Knowledge of relevant comorbid conditions can aid in understanding disease course, its impact, and may assist in mitigating effects
- Food, drugs, stress, and infections have signals that can trigger CSU exacerbations
- No routine testing for conditions that modify disease activity should be performed – further diagnostic tests listed in Table II should be considered

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?	TSH, fT4, if indicated IgG anti-TPO
	• Signs or symptoms suggestive of hyper- or hypothyroidism	
Mental disorders	• Do you feel depressed?	HADS, CU-Q2oL, if indicated referral to specialist
	• Do you feel overly anxious?	
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.

- 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

Summary

- Initial diagnostic testing should include CRP, ESR, and CBC with differential with the focus being on confirming diagnosis
- Physicians should explore patients with CSU for underlying causes by asking relevant questions and reserve more specific tests only when indicated
- No routine testing for conditions that modify disease activity is recommended
- No routine testing should be performed for possible comorbidities and consequences
- There are no definitive predictors of disease duration, activity, or response to treatment

Discussion

- Current evaluation of patients with CSU is driven by a thorough history with further diagnostic testing being reserved for patients with specific elements in their disease course
- Asking appropriate questions will prevent unnecessary and potentially expensive testing and increase diagnostic accuracy and treatment effectiveness
- Further research aimed at identifying lab markers associated with disease duration and activity may help in counseling patients in the future