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BRIEF COMMUNICATION

Practical algorithm for diagnosing patients with recurrent wheals or angioedema

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Abstract

Background: Chronic urticaria is a common disorder characterized by recurrent wheals, angioedema, or both. Several differential diagnoses need to be considered in patients presenting with wheals and/or angioedema. These include rare diseases such as autoinflammatory syndromes and urticarial vasculitis in patients with recurrent wheals and bradykinin-mediated angioedema in patients with recurrent swellings.

Aim and Result: In order to not miss these conditions, we have developed a symptom-based diagnostic algorithm for the management of patients with wheals and/or angioedema.

Discussion and Conclusion: By asking the right questions and performing a limited diagnostic workup as suggested here, this algorithm may help to establish the right diagnosis and treat patients early and more effectively.

Recurrent wheals (also called hives) and angioedema, that is, superficial and deep skin swellings, respectively, are common signs in patients seen by general practitioners and specialists including dermatologists, allergists, ENTs, and pediatricians. Recurrent wheals and angioedema are usually the signs of urticaria, especially when both of them occur in the same patient. Urticaria, by definition, is the occurrence of wheals and/or angioedema (1).

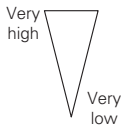
There are, however, conditions other than urticaria that can manifest with wheals or angioedema. These include urticarial vasculitis and autoinflammatory disorders such as Schnitzler syndrome or cryopyrin-associated periodic syndromes (CAPS) in patients with recurrent wheals and bradykinin-mediated angioedema in patients with recurrent angioedema (Table 1). These conditions are much less frequent than urticaria and, therefore, are commonly missed or misdiagnosed, resulting in long delays of correct diagnosis (2). In general, these differential diagnoses of chronic urticaria (>6 weeks duration) are characterized by their persistence, markedly impaired quality of life, and increased mortality. Urticaria medication such as antihistamines is frequently used, but usually ineffective in these disorders.

For all these reasons, it is important to consider, in all patients with wheals or angioedema, conditions other than urticaria. In routine clinical practice, this may be facilitated by the use of a symptom-based diagnostic algorithm (Fig. 1). In patients with recurrent wheals and angioedema, urticaria is the most likely diagnosis. None of the bradykinin-mediated forms of angioedema present with wheals (3), and angioedema is a rare and untypical symptom in patients with wheals due to autoinflammatory disorders (4). Angioedema may, however, be present in a subset of patients with urticarial vasculitis (5).

How to look for underlying causes in patients with recurrent wheals

Patients with recurrent wheals without angioedema should be checked for autoinflammatory conditions and urticarial vasculitis as the cause of their symptoms. Autoinflammatory disorders are rare multisystemic, interleukin-1-driven inflammatory diseases mediated primarily via innate immune responses (6). Clinically, they often manifest with wheals, recurrent bouts of unexplained fever, and pain of the joints, muscles, and/or bones. This is usually accompanied by a general sense of 'feeling ill'. Patients with wheals should, therefore, be asked: 'Do you sometimes have a fever without any apparent reason? Do your joints or bones hurt or do you have pain anywhere else? Do you feel ill or exhausted?' Affirmative

Table 1 Classification of disorders that present with recurrent wheals only, both wheals and angioedema, and angioedema only

Wheals only	Wheals and angioedema	Angioedema only	Frequency of disorders
CSU	CSU	CSU	
CINDU*	CINDU**	DPU	
Urticarial vasculitis	Urticarial vasculitis	ACE-I-induced angioedema	
Autoinflammatory disorders		HAE	
		AAE	

AAE: angioedema due to acquired C1-inhibitor (C1-INH) deficiency; CSU: chronic spontaneous urticaria; CINDU: chronic inducible urticaria; DPU: delayed pressure urticaria; HAE: hereditary angioedema.
*Excluding DPU, which does not present with classical wheals; **Excluding symptomatic dermographism and cholinergic urticaria, which do not present with angioedema.

answers should prompt further questions and investigations (particularly inflammation markers) to confirm or rule out autoinflammatory disease. The diagnostic approach for this has recently been described in detail (4). Most importantly, hereditary periodic fever syndromes, in particular the cryopyrin-associated periodic syndromes (CAPS: familial cold autoinflammatory syndrome [FCAS], Muckle–Wells syndrome [MWS], and neonatal-onset multisytem inflammatory disease [NOMID]), should be looked for by a detailed family history, age of disease onset (<20 years), and genetic testing of the NLRP3 gene (7), if applicable, and Schnitzler syndrome (adult onset) should be checked for by serum immune fixation for the detection of monoclonal gammopathy (8).

In addition to CAPS and Schnitzler syndrome, urticarial vasculitis (UV) is an important differential diagnosis to consider in patients with recurrent wheals. Patients with UV may also report intermittent joint pain as well as malaise or even fever. UV typically manifests with wheals of longer than 24-h duration. In many patients with UV, but not all, the wheals resolve with transient hematoma and hyperpigmentation, which is not seen in urticaria. The lead question to rule out UV is, therefore: 'How long do your wheals last?' In patients with wheals of more than 24-h duration, UV should be suspected and checked for by histopathological assessment of a skin biopsy from a wheal. Histological signs of UV such as leukocytoclastic vasculitis with damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations confirm UV (9). In contrast, most cases of autoinflammatory disease show dense neutrophil-rich perivascular and interstitial infiltrates typically without signs of leukocytoclasis in lesional skin (10). If no signs of UV are seen histologically and if individual wheals are of <24-h duration, urticaria may be assumed to be the underlying disease responsible for the wheals.

Chronic urticaria (i.e., wheals and/or angioedema that occur for longer than 6 weeks) can either be spontaneous or inducible. The diagnostic workup and the therapy of chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU) are quite different. The most important first question to patients with chronic urticarial rash, therefore, is: 'Can you make your wheals come?' This will allow to distinguish CINDU ('yes') from CSU ('no'). Patients suspected to have CINDU should be investigated for specific trigger(s) of wheal induction (e.g., skin contact with cold water in cold urticaria; exercise or sauna/hot bath in cholinergic urticaria) and offered provocation testing if possible. Patients with CINDU should be asked whether their symptoms sometimes appear even though they are not exposed to a relevant trigger. If this is the case, patients are likely to also have CSU.

How to look for underlying causes in patients with recurrent angioedema

Recurrent angioedema without wheals should prompt suspicion of bradykinin-mediated angioedema, which can be hereditary or acquired. One of the latter forms of angioedema, that is, angiotensin-converting enzyme inhibitor (ACE-I)-induced angioedema, is readily diagnosed by simply asking patients whether they are taking an ACE-I. Angioedema in patients with ACE-I is ACE-I induced, unless proven otherwise. The close correlation between ACE-I intake and onset of recurrent angioedema was recently verified in a long-term observational study in hypertensive patients receiving ACE-I treatment (11). ACE-I medication should be discontinued in all patients with recurrent angioedema, even if swellings first occur years after the start of ACE-I treatment (12). Remission of angioedema attacks after stopping ACE-I medication confirms ACE-I-induced angioedema, but may not occur for several months after the last ACE-I intake. Patients with ACE-I-induced angioedema should refrain from using this class of drugs in the future.

Patients with recurrent angioedema who do not use ACE-I should be asked for a detailed family history and checked for hereditary bradykinin-mediated angioedema (HAE I-III) and angioedema due to acquired C1-inhibitor (C1-INH) deficiency (AAE) (13). Normal complement C4 levels, normal C1-INH function and protein levels, the absence of C1-INH antibodies and relevant mutations in the C1-INH or factor XII gene, and efficacy of antihistamines, glucocorticoids or adrenaline all argue against HAE or AAE and should prompt suspicion of urticaria (spontaneous or inducible, depending on the relevance of a trigger) as the underlying cause of the recurrent swellings. Up to 10% of patients with CSU are reported to present with recurrent angioedema, but not wheals. Antihistamine-resistant angioedema with neither a history of ACE-I intake nor C1-INH deficiency has been classified as idiopathic angioedema by some authors. However, a diagnosis of

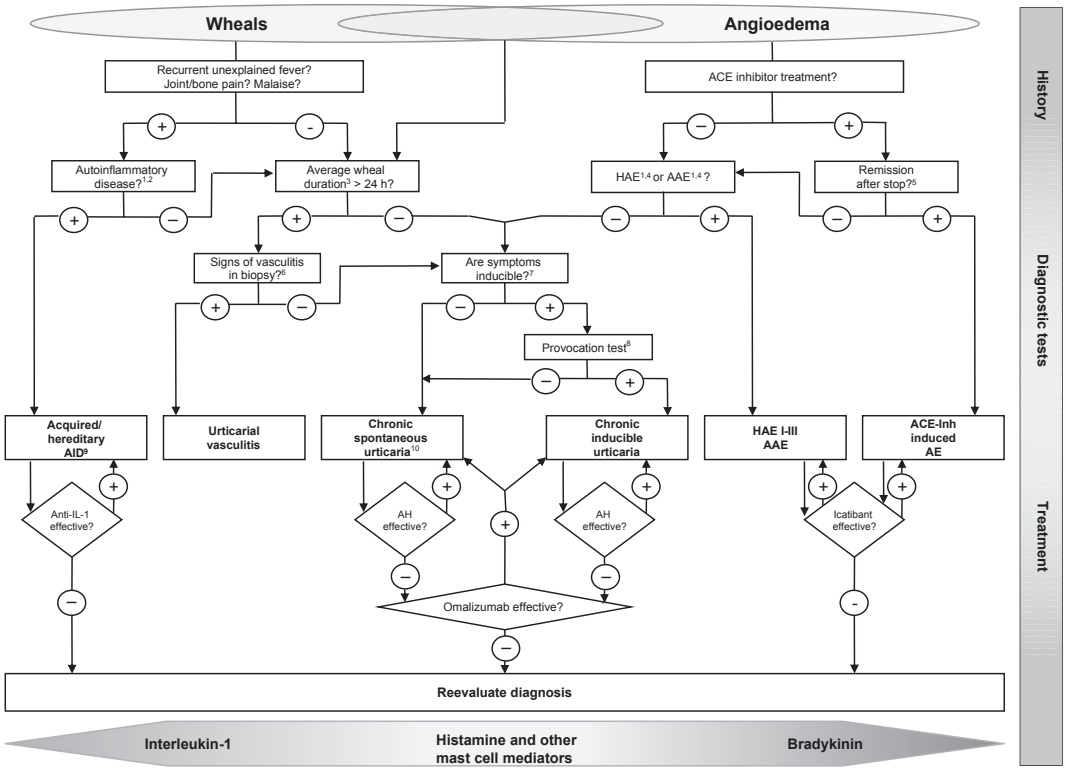


Figure 1 Diagnostic algorithm for patients presenting with wheals only, wheals and angioedema, and angioedema only. A short form of this algorithm was discussed and agreed by the 4th International Consensus Meeting on Urticaria 'URTICARIA2012' in November 2012 in Berlin. AAE: acquired angioedema due to C1-inhibitor deficiency; ACE-Inh: angiotensin-converting enzyme inhibitor; AE: angioedema; AH: antihistamine; AID: autoinflammatory disease; HAE: hereditary angioedema; IL-1: interleukin-1. [1]Patients should be asked for a detailed family history and age of disease onset. [2]Test for elevated inflammation markers (C-reactive protein, erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis of hereditary periodic fever syndromes (e.g., cryopyrin-associated periodic syndrome), if strongly suspected. [3]Patients should be asked: 'How long do your wheals last?' [4]Test for complement C4 levels and C1-INH levels and function; in addition, test for C1q and C1-INH antibodies, if AAE is suspected; carry out gene mutation analysis, if former tests are unremarkable but patient's history suggests hereditary angioedema. [5]Wait for up to 6 months for remission; additional diagnostics to test for C1-inhibitor deficiency should only be performed, if the family history suggests hereditary angioedema. [6]Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of UV? If yes, direct immunofluorescence should be performed to look for immune complexes (immunoglobulins or complement) in vessel walls. Also, if suggested by the history, systemic vasculitic diseases that may present with UV (e.g., lupus erythematosus or Sjögren's syndrome) should be ruled out and patients should be screened for antinuclear and extranuclear antibodies where indicated. [7]Patients should be asked: 'Can you make your wheals come?' [8]In patients with a history suggestive of inducible urticaria, standardized provocation testing according to international consensus recommendations (16) should be performed. [9]Acquired AIDs include Schnitzler syndrome as well as systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD); hereditary AIDs include cryopyrin-associated periodic syndromes (CAPS) such as familial cold autoinflammatory syndromes (FCAS), Muckle–Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID), more rarely hyper-IgD syndrome (HIDS) and tumor necrosis factor receptor alpha–associated periodic syndrome (TRAPS). [10]In some rare cases, recurrent angioedema is neither mast cell mediator mediated nor bradykinin mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as 'idiopathic angioedema' by some authors.

idiopathic angioedema should only be made after thorough evaluation and exclusion of all relevant causes (14).

What can we learn from patients' responses to treatment?

Nonsedating antihistamines, at standard or higher-than-standard doses, alone or in combination (e.g., with a leukotriene antagonist and an H2 blocker) are commonly used to prevent wheals and angioedema in patients with urticaria (15). Failure to respond to these treatments and especially inefficacy of omalizumab should raise suspicion of autoinflammatory disorders or UV in patients with wheals and of bradykinin-mediated angioedema in patients with angioedema. Vice versa, failure of autoinflammatory disorders to respond to IL-1-targeting drugs is extremely rare as is failure of bradykinin-induced angioedema

to be controlled by icatibant, a specific bradykinin B2 receptor antagonist.

In conclusion, autoinflammatory disorders, urticarial vasculitis, and bradykinin-mediated angioedema are rare differential diagnoses of chronic urticaria that should be kept in mind when seeing patients with wheals or angioedema in clinical practice. Our diagnostic algorithm may guide physicians in their diagnostic approach and may help to treat patients more effectively.

Conflict of interest

The authors declared no conflict of interest in relation to this work.

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