

Differentiating histaminergic and nonhistaminergic angioedema with or without urticaria



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Angioedema (AE) is a relatively common symptom and can occur alone or with associated wheals, a condition commonly known as urticaria. Urticaria is characterized by the development of wheals (hives), AE, or both.¹ AE disorders with different underlying pathophysiology may have a similar clinical appearance; therefore, the differential diagnosis of AE represents a challenge for the treating physician. Misdiagnosis and delay in the correct diagnosis increases mortality and morbidity and leads to unnecessary medical interventions and inappropriate medical treatments.

AE is defined as transient, recurrent swelling of subcutaneous and/or submucosal tissue, commonly involving the mucous membranes in the upper respiratory or the gastrointestinal (GI) tract. AE is a consequence of increased local permeability in the subcutaneous or submucosal capillaries and postcapillary venules, causing local plasma extravasation in response to vasoactive mediators released from activation of mast cells and/or basophil granulocytes or the contact (kinin-kallikrein), complement, and fibrinolytic plasma enzyme systems. On the basis of the vasoactive mediators involved in the process, AE conditions have 2 primary forms according to the current classification: histaminergic (mast cell-mediated) and nonhistaminergic (predominantly bradykinin-mediated). In clinical practice, these 2 types of AE may be separated by the response to conventional therapy (acute treatment with antihistamines, glucocorticoids, and epinephrine, as well as prophylactic treatment with high-dose antihistamines

and in some settings, with omalizumab). Histaminergic forms generally respond well to conventional treatment and are usually associated with wheals/urticaria, whereas nonhistaminergic forms do not respond to this treatment and occur without wheals or urticaria. The hereditary forms of nonhistaminergic AE also often show a clear inheritable pattern. Although nonhistaminergic AE is less common, 13 types have currently been described. Revision of the current AE classification system published in 2014 became necessary owing to several factors. As molecular genetic technologies have improved, further forms of AE were discovered. All forms of hereditary AE (HAE) with normal C1 inhibitor (nC1-INH-HAE) are classified as nonhistaminergic forms, although on the basis of current knowledge, bradykinin appears to be the predominant vasoactive mediator in some of these forms (eg, HAE with FXII mutations, HAE with plasminogen mutations, and HAE with kininogen 1 mutations), whereas the pathophysiology of HAE with angiotensin-converting enzyme (ACE) mutations, HAE with myoferlin mutations, and HAE with heparan sulfate 3-O-sulfotransferase 6 mutations, is less well established and may involve other mechanisms of vascular leak.^{2,3} Moreover, several other permeability-modifying factors besides bradykinin play a role in nonhistaminergic AEs. Thus, classification based on endotypes may be more accurate than phenotype-based classification. For diagnosing and treating histaminergic and nonhistaminergic AEs, international guidelines provide state-of-the-art recommendations.^{1,3,4}

A diagnostic algorithm helps establish a correct diagnosis by carefully evaluating the nature of clinical symptoms, family history, response to medications, and laboratory test results.

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EVALUATION OF SYMPTOMS

In general, the concurrence of urticaria and AE is a characteristic of histaminergic forms, although clinically these 2 symptoms do not necessarily occur at the same time. Nonhistaminergic AE is not accompanied by urticaria, and AE attacks are often preceded by prodrome symptoms (erythema marginatum, pain, tiredness, or nausea), especially in HAE with C1 inhibitor deficiency (C1-INH-HAE).⁵

Time of the appearance of symptoms

Histaminergic forms may occur at any age, whereas in nonhistaminergic conditions, the onset of symptoms may follow more specific patterns. In C1-INH-HAE, the first symptoms usually occur in childhood (by the age of 10 to 12 years); in nC1-INH-HAE, they occur in young adults, whereas in cases of acquired AE (AAE) with C1 inhibitor deficiency (C1-INH-AAE) and AAE related to angiotensin-converting enzyme inhibitor (ACEI-AAE), symptoms mainly occur after 40 years of age. In ACEI-AAE, AE may occur a few hours after ACEI treatment or

develop after many years of symptom-free treatment with an ACEI.

Localization of symptoms

Symptoms may occur at a single anatomic site or multiple locations simultaneously. The location of symptoms is similar in both forms, but there may be differences between the subgroups in terms of the frequency of anatomic site involvement.

Subcutaneous localization. Subcutaneous edema may occur in the head and/or neck, trunk, extremities, or external genitalia. AE of the extremities occurs most frequently in C1-INH-HAE, but it is the second most common AE site in histaminergic AE as well. Edema on the face or genitalia occurs in 3% and 4% of all AE attacks, respectively; however, 80% of patients with C1-INH-HAE will experience facial AE, and 33% will experience genital AE.⁵

Submucosal localization. *Upper respiratory tract.* Pharyngeal and laryngeal AE may cause difficulty swallowing and breathing, with risk of suffocation. These complications are much more frequent in nonhistaminergic AE, but they may also occur as part of histaminergic, IgE-mediated anaphylactic shock.⁵

Tongue involvement is frequent in histaminergic AE and nC1-INH-HAE, and it is especially characteristic of HAE with plasminogen mutations and ACEI-AAE. Isolated involvement of the tongue in C1-INH deficiency is rare.⁵

GI tract. AE occurring in the GI mucosa is primarily a characteristic of nonhistaminergic forms. More than 90% of patients with C1-INH-HAE experience GI AE attacks that can be accompanied by intense abdominal pain, nausea, vomiting, diarrhea, and hypovolemic shock. To differentiate GI AE episodes from other abdominal conditions, imaging techniques are helpful, with demonstration of free intraperitoneal fluid and bowel edema during an abdominal attack. GI involvement is rare in histaminergic AE.⁵

Symptom duration

Similar to urticaria, histaminergic AEs can be divided into 2 groups based on the duration of recurrent symptoms: if AE episodes recur for less than 6 weeks, it may be considered acute. AE episodes recurring for more than 6 weeks may be considered chronic recurrent.^{1,5} Acute AE with urticaria may be IgE-mediated, with the AE and urticaria occurring within 30 to 60 minutes after allergen exposure, progressing rapidly, and improving or resolving within 12 to 24 hours in most cases, although AE symptoms sometimes take up to 48 hours to fully resolve. In chronic recurrent AE, as with chronic urticaria, the underlying cause of symptoms is often enigmatic; however, the episodic AE symptoms generally do not exceed 24 to 48 hours in duration. In nonhistaminergic forms, the AE attack develops more slowly, often taking 24 hours to reach maximal severity, and it usually lasts for 1 to 5 days, but in more severe cases, it persists for up to a week.⁵

PROVOKING FACTORS

For histaminergic forms of acute AE, provoking factors for investigation include food, insect bites or stings, medications, environmental allergens, physical stimulus, and infection.

However, for recurrent AE that becomes chronic (recurring episodes for >6 weeks), these factors are much less likely to be the underlying cause of symptoms without a clear history identification of such triggers. In nonhistaminergic forms, the initiating event for attacks is often unknown, although common trigger factors include psychological stressors, mechanical trauma, hormonal effects (puberty, menstruation, or pregnancy), medication, infections, other accompanying diseases, or surgical interventions.⁵ In nC1-INH-HAE, the first occurrence or worsening of symptoms in women can often be dated to the introduction of estrogen-containing oral contraceptives or can happen during menstruation or pregnancy. ACEI- or estrogen-containing medications can be provoking factors mainly in non-histaminergic forms.⁵

FAMILY HISTORY

If the family history is positive for AE, HAE should be strongly considered. However, the lack of a family history does not exclude some forms of HAE, given demonstrated *de novo* mutations. This can make it difficult to separate autosomal dominant inherited and acquired forms of AE, because the genetic cause develops spontaneously in some patients and their family history is negative for AE. In 25% of C1-INH-HAE cases, spontaneous mutations occur. Currently, there are no data on the rate of *de novo* mutations in nC1-INH, and owing to low penetrance, symptoms do not always manifest in spite of the gene defect being present.^{6,7}

LABORATORY TESTS AND EVALUATION OF RESULTS

Often, initial diagnostic clues are based on clinical response to previous conventional treatment with antihistamines, systemic corticosteroids, and/or epinephrine. If the AE responds to conventional treatment, the histaminergic form of AE should be presumed. Significant improvement in the frequency and/or severity of recurrent angioedematous episodes (with or without urticaria) with administration of daily continuous antihistamine treatment (often requiring dose increases to quadruple the standard dose) or with omalizumab treatment is consistent with histaminergic AE. In addition to a detailed medical history, it can be beneficial to explore trigger factors and consider basic laboratory tests if indicated on the basis of clinical history (eg, complete blood count, C-reactive protein level, total IgE level, and anti-thyroid peroxidase IgG level) (Table 1). When the cause of AE is not an identifiable factor, the condition is classified as idiopathic histaminergic acquired AE (IH-AAE)/chronic spontaneous urticaria.^{1,3}

If treatment with high-dose second-generation antihistamines and/or omalizumab is not successful in treatment of AE attacks or prevention of their recurrence, laboratory evaluation of the complement system is recommended. It can be argued that such testing should be considered in any patient with AE in the absence of urticaria/wheals to more rapidly identify individuals with C1-INH deficiency. In addition to C1-INH antigenic concentration and functional activity, C4, C1q, and anti-C1-INH antibody levels are helpful in certain clinical scenarios. In C1-INH-HAE type 1, the antigenic level of C1-INH and its activity are decreased, whereas in C1-INH-HAE type 2, the level of C1-INH antigen is normal or increased but functional activity is low.

TABLE I. Recommended tests in different types of AE

AE type			Routine diagnostic tests (recommended)	Extended diagnostic pro- gram (based on history)*
Histaminergic AE	Acute	IgE-mediated	None	None
		Non-IgE-mediated	None	None
	Chronic	Inducible	Cold urticaria	Cold provocation and threshold test
			Delayed pressure urticaria	Pressure test and threshold test
			Heat urticaria	Heat provocation and threshold test
			Solar urticaria	UV and visible light of different wavelengths and threshold test
			Symptomatic dermographism	Elicit dermographism and threshold test
			Vibratory AE	Test with vibration
			Aquagenic urticaria	Use a wet cloth at body temperature for 20 min
			Cholinergic urticaria	Exercise and hot bath provocation
			Contact urticaria	Skin tests (eg, prick test, prick by prick test)
			Spontaneous urticaria or IH-AAE†	Differential blood count, ESR and/or CRP
				IgG anti-TPO and total IgE
Nonhistaminergic AE	Hereditary	With C1-inhibitor deficiency	C1-INH-HAE type I	Complement laboratory tests‡
			C1-INH-HAE type II	
		With normal C1-inhibitor function	FXII-HAE	Complement laboratory tests,‡ genetic tests
			PLG-HAE	
			ANGPT1-HAE	
			KNG1-HAE	
			MYOF-HAE	
			HS-HAE	
			U-HAE	
	Acquired	With C1-inhibitor deficiency	C1-INH-AAE type I	Complement laboratory tests‡
			C1-INH-AAE type II	
		With normal C1-inhibitor function	ACEI-AAE (taking an ACEI)	
			InH-AAE	

Data from Zuberbier et al¹ and Maurer et al.³

ACEI, Angiotensin-converting enzyme inhibitor; ANGPT1-HAE, HAE with angiotensin I mutations; CindU, chronic inducible urticaria; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; FXII-HAE, HAE with FXII mutations; HS-HAE, HAE with heparan sulfate 3-O-sulfotransferase 6 mutations; IH-AAE, idiopathic histaminergic acquired AE; InH-AAE, idiopathic nonhistaminergic acquired AE, KNG1-HAE, HAE with kininogen 1 mutations; MYOF-HAE, HAE with myoferlin mutations; PLG-HAE, HAE with plasminogen mutations; TPO, thyroid peroxidase; U-HAE, HAE with unknown origin.

*For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated.

†The definition of CSU is used mainly by urticaria specialists (in this case, urticaria can present with or without AE). IH-AAE is the name used in the classification of AE.^{1,2}

‡C4 level, C1-INH antigen, C1-INH function, C1q level.

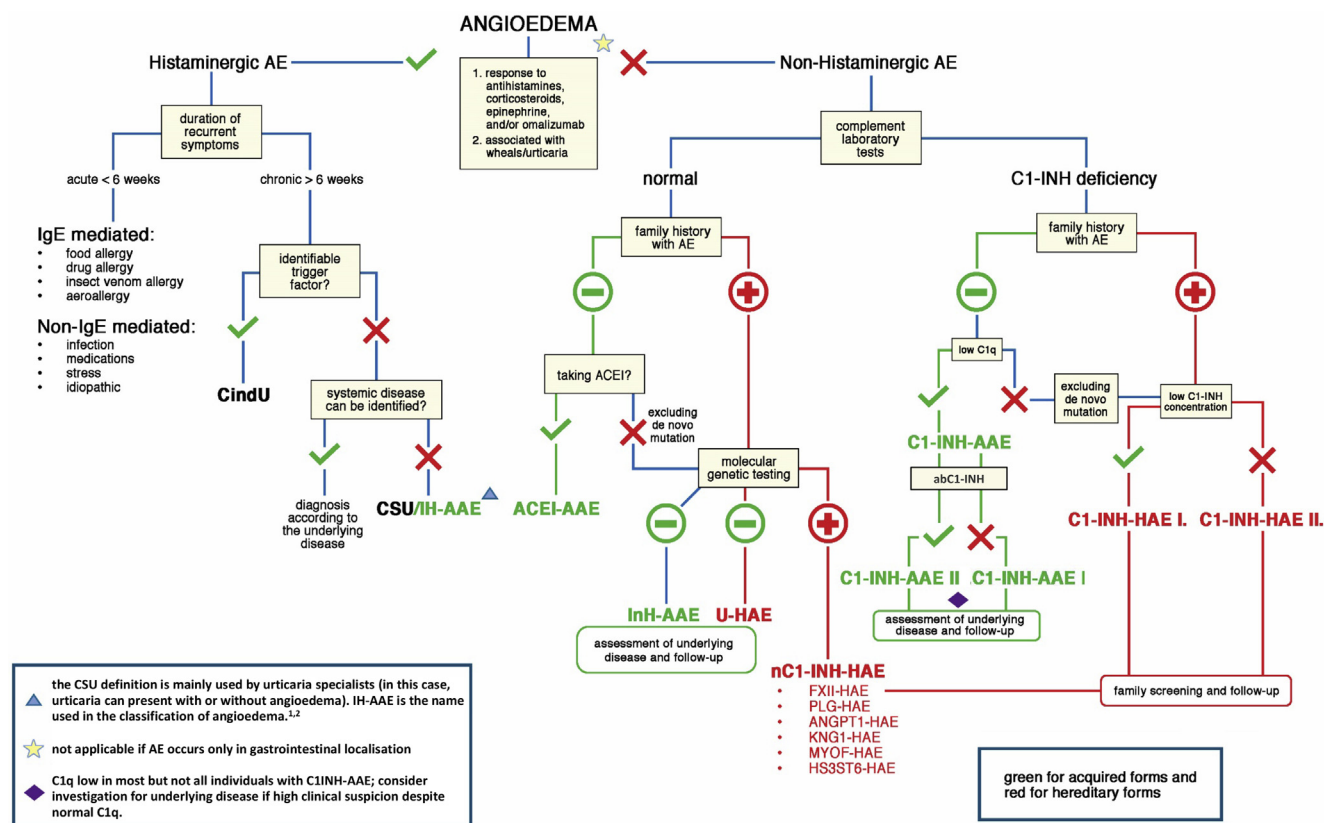


FIG 1. Algorithm for the investigation of AE. *ANGPT1-HAE*, HAE with angiopoietin1 mutations; *CindU*, chronic inducible urticaria; *CSU*, chronic spontaneous urticarial; *FXII-HAE*, HAE with FXII mutations; *HS3ST6-HAE*, HAE with heparan sulfate 3-O-sulfotransferase 6 mutations; *IH-AAE*, idiopathic histaminergic acquired AE; *InH-AAE*, idiopathic nonhistaminergic acquired AE, *KNG1-HAE*, HAE with kininogen 1 mutations; *MYOF-HAE*, HAE with myoferlin mutations; *PLG-HAE*, HAE with plasminogen mutations; *U-AAE*, HAE with unknown origin.

In C1-INH-HAE, the level of C4 is decreased (persistently in most cases, but invariably during AE episodes) and the C1q level is normal. In C1-INH-AAE, the C1-INH antigenic concentration and activity are decreased and the level of C4 and C1q are also commonly decreased; in some cases, anti-C1-INH antibodies (IgG, IgM, and IgA) can be detected.^{7,8}

If AE episodes occur while the patient is taking ACEI medications, it can present difficulties in the differential diagnosis. The international European Academy of Allergy and Clinical Immunology/Global Asthma and Allergy European Network/European Dermatology Forum Guideline/Asia Pacific Association of Asthma, Allergy, and Clinical Immunology guideline recommends that if AE occurs beyond 6 months after discontinuation of ACEI treatment, complement testing should be performed.¹ Newer studies support complement testing for patients taking ACEI medication and showing AE symptoms, because ACEIs can exacerbate AE in both acquired and hereditary forms of C1-INH deficiency. If complement parameters are normal and the family history is negative, the diagnosis of ACEI-AAE can be presumed.⁹

If the result of complement testing excludes C1-INH deficiency and the family history is positive for AE, genetic testing is

necessary to diagnose various forms of nC1-INH-HAE (Fig 1). If the results of complement and genetic tests are negative in an individual with a clinical phenotype of nonhistaminergic AE but family members with AE can be identified, the patient may be diagnosed with HAE with unknown origin.^{4,7} If genetic studies do not show pathologic mutations and the family history is negative for AE, idiopathic nonhistaminergic AAE (InH-AAE) is most likely.^{7,8,10} If any form of HAE is diagnosed, family members should be tested by complement and/or genetic testing to confirm or exclude the disease. If C1-INH-AAE is diagnosed, investigation for underlying malignancy (most often, lymphoproliferative conditions), autoimmune disorders, or infectious disorders is necessary.^{7,8}

Differentiation of the types of AEs may be challenging, requiring a detailed medical history and following diagnostic algorithms to successfully navigate the differential diagnosis. It is important to follow the symptoms of patients with AE and their response to the treatment, which provides opportunities to reevaluate the diagnosis and modify the therapy. Thanks to the discovery of new genetic techniques and laboratory biomarkers, the classification and diagnostic algorithm of AE continue to evolve, requiring relevant timely updates to clinical guidelines.

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