

NEWS & VIEWS

Algorithms in Allergy and Clinical Immunology

Medical algorithm: Diagnosis and management of histaminergic angioedema

Angioedema is defined as a self-limited swelling of the deep dermis, subcutaneous, and/or submucosal tissue due to the action of vasoactive mediators.¹ Depending on the mediator involved, it is classified as either bradykinin-mediated or histamine-mediated. The designation of histaminergic angioedema or idiopathic histaminergic acquired angioedema² could lead one to think that it has to respond to antihistamines, but this is not the case.³ The term mast cell-mediated angioedema (MC-AE) would be more appropriate to include patients for whom antihistamine therapy is insufficient. However, the term should be agreed upon in the next guidelines.

We aim to offer some guidance and clues to correctly diagnose patients who present with recurrent episodes of isolated MC-AE with no hives.

In the European guideline, histaminergic angioedema (HA) is defined as acquired recurrent angioedema with or without hives with no underlying cause that is controlled with antihistamines, corticosteroids, adrenaline, and omalizumab.⁴ HA is considered to be a subtype of chronic spontaneous urticaria (CSU) but without hives. We have demonstrated⁵ in a population of patients suffering from isolated HA compared to a population with CSU plus angioedema that several key features differentiate HA from CSU, including different gender distribution and the absence of basopenia or antibodies against the IgE receptor in HA. It is our position that HA should be considered a separate entity, and future

guidelines should at least consider this alternative. Nevertheless, the angioedema of HA is clinically identical to the angioedema that can accompany CSU, although HA does not evolve into a combination of urticaria and angioedema. Occasionally, in clinical practice, one can observe patients starting with isolated angioedema and later on evolving to angioedema with hives, although data about those are scarce.

It is extremely important to differentiate HA from bradykinin-mediated angioedema (BK-AE), not only because the treatments are different but also because BK-AE could be life-threatening and should be promptly identified.

The C4 level can be a potential biomarker for hereditary angioedema (HAE) given a history of recurrent angioedema. Abnormal C1-INH levels or activity are required to specifically diagnose HAE Types I and II. However, there are rare forms of HAE in which C1-INH levels or activity are normal and are caused by different mutations. Although uncommon, occasional patients suffering from HA may have a familial background of angioedema.^{5,6} The most common way to identify HA as opposed to BK-AE is the response to treatment during acute episodes employing antihistamines, corticosteroids, and/or adrenaline, whereas BK-AE may respond to C1-INH replacement therapy, bradykinin antagonists, or plasma kallikrein inhibitors. In the Table 1, we summarize the key differences between HA and BK-AE. Additionally, the treatment response should be

TABLE 1 Clinical and serological differences between Histaminergic and Bradikineric angioedema

Angioedema	Histaminergic angioedema	Bradikineric angioedema
Episode duration	12–36 h	>36 h
Erythema Marginatum	No	Yes (is limited to C1-INH HAE and mostly not observed in other forms)
Oropharyngeal swelling	Yes	Yes
Laryngeal edema	Rare	Frequent
Abdominal pain attacks	No	Yes
C4/C1-INH protein and function	Normal	Deficient ^a
Familial	No, rare positives ^b	Yes (75%)

Abbreviations: C4, complement factor 4; C1-INH, complement factor 1 inhibitor.

^aThere is a small group of patients with normal C1-INH levels or function, in which angioedema is caused by other known mutations (7 to date).

^bIn some instances patients suffering from histaminergic angioedema have familial background.

Abbreviations: BK-AE, bradykinin-mediated angioedema; C1-INH, complement factor 1 inhibitor; C4, complement factor 4; CSU, chronic spontaneous urticaria; HA, histaminergic angioedema; MC-AE, mast cell-mediated angioedema.

assessed by comparing the absence of or decrease in the number of angioedema episodes to the untreated scenario, with regular, supra-therapeutic doses of antihistamines and if no response is achieved,

with omalizumab. It is important to keep in mind that sometimes, in clinical practice, the acute response to AH, corticosteroids or adrenaline is unclear in some patients with a true mast cell-mediated

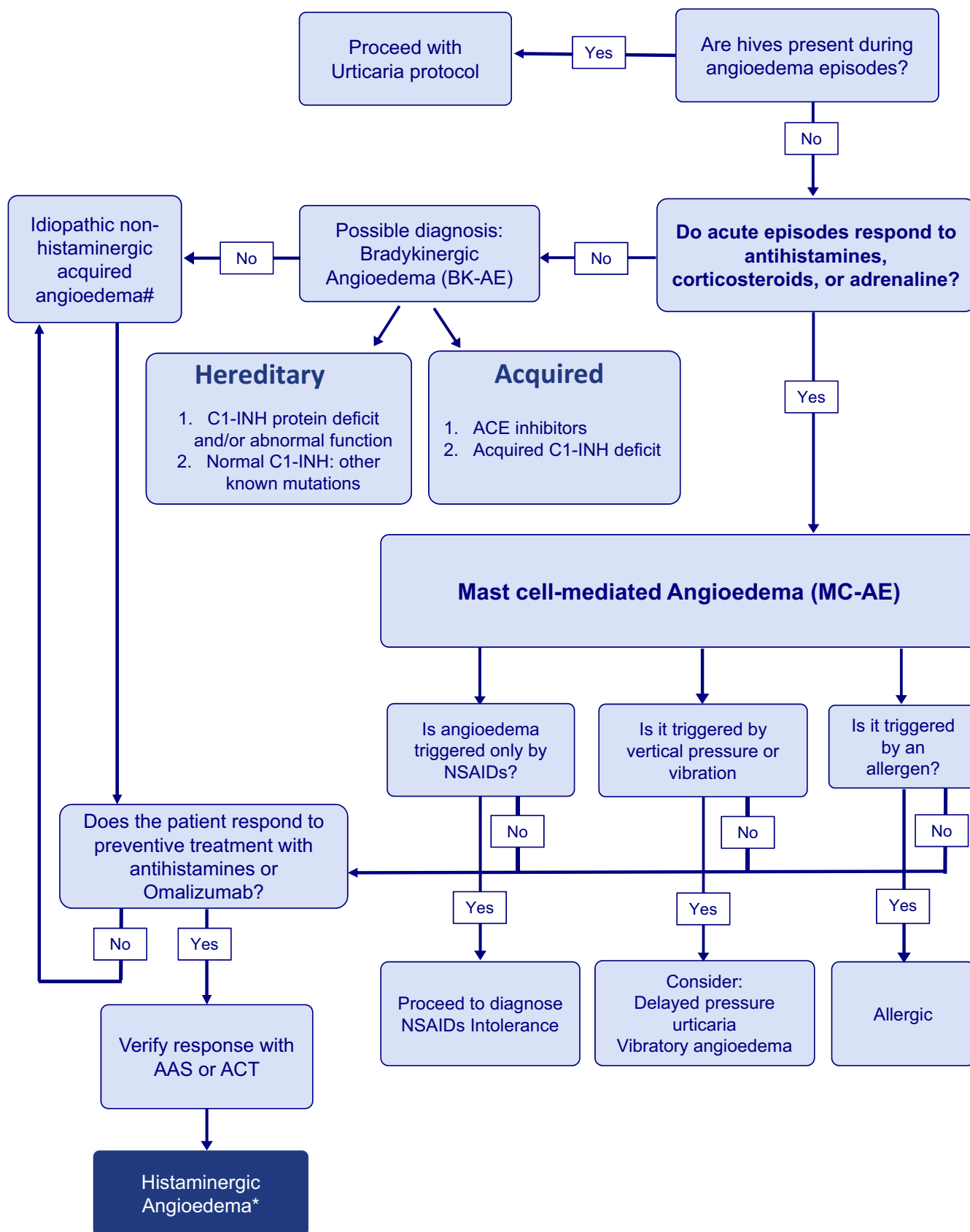


FIGURE 1 Diagnostic and management algorithm for histaminergic angioedema. ACE, angiotensin-converting enzyme; C1-INH, complement factor 1 inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; AAS, Angioedema Activity Score; ACT, Angioedema Control Test. *The fact that patients may respond to preventive treatment with omalizumab but not to antihistamines reflect the diversity of mediators involved in MC-AE. #Some patients labelled as idiopathic non-histaminergic acquired angioedema respond to treatments for either MC-AE or BK-AE, suggesting that the label may be wrongly used on some occasions. Adapted from Maurer et al. Allergy The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022 Jul;77(7):1961–1990.

angioedema, who respond only to prophylaxis/treatment with omalizumab. These patients are often mislabeled as idiopathic non-histaminergic angioedema. The frequency of HA episodes can vary from once or twice a year to more than one episode per week. For that reason, preventive treatment may need to be maintained for a prolonged time to evaluate efficacy. Validated questionnaires such as the Angioedema Activity Score⁷ or the Angioedema Control Test⁸ should be used to monitor treatment efficacy more precisely.

In addition to different entities that could mimic HA,⁹ other types of MC-AE should be considered. Infrequently, cross-intolerance nonsteroidal anti-inflammatory drugs could present as isolated angioedema usually involving the face. MC-AE could be present within the context of some chronic inducible urticarias. MC-AE due to food or drug allergic reactions is very uncommon in the absence of hives or other allergic symptoms such as abdominal pain, bronchospasm, or anaphylaxis.

Given the difficulty of differentiating HA from other forms of non-histaminergic angioedema, it is important to highlight the role of omalizumab response as a key HA marker. It is never the case of non-histaminergic angioedema and the decrease or disappearance of angioedema episodes in HA (or MC-AE) is often dramatic.^{10,11} We provide in the [Figure 1](#) the diagnosis and management approach suggested.

There are several unmet needs for HA (1) to clarify its nomenclature and classification, (2) to define criteria to evaluate treatment response in an acute setting, and (3) to find biomarkers that distinguish BK-AE from HA. An assay has been reported¹² that may identify BK-AE. Finally, the exact physio-pathological mechanisms remain to be defined.

KEYWORDS

bradykinin-mediated angioedema, histaminergic angioedema, mast cell-mediated angioedema

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CONFLICT OF INTEREST

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REFERENCES

- Kaplan AP. Angioedema. *World Allergy Organ J*. 2008;1(6):103–113.
- Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the hereditary angioedema international working group. *Allergy*. 2014;69(5):602–616.
- Caballero T, Ferrer M, Guilarte M. Classification and treatment of angioedema without wheals: a Spanish Delphi consensus. *Am J Clin Dermatol*. 2022. doi:10.1007/s40257-022-00735-7
- Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2021 revision and update. *Allergy*. 2022;77(7):1961–1990.
- Sabaté-Brescó M, Rodríguez-Garijo N, Azofra J, et al. A comparative study of sex distribution, autoimmunity, blood, and inflammatory parameters in chronic spontaneous urticaria with angioedema and chronic histaminergic angioedema. *J Allergy Clin Immunol Pract*. 2021;9(6):2284–2292.

6. Can PK, Degi Rmentepe EN, Etikan P, et al. Assessment of disease activity and quality of life in patients with recurrent bradykinin-mediated versus mast cell-mediated angioedema. *World Allergy Organ J.* 2021;14(7):100554.
7. Weller K, Groffik A, Magerl M, et al. Development, validation, and initial results of the angioedema activity score. *Allergy.* 2013;68(9):1185-1192.
8. Weller K, Donoso T, Magerl M, et al. Development of the angioedema control test-a patient-reported outcome measure that assesses disease control in patients with recurrent angioedema. *Allergy.* 2020;75(5):1165-1177.
9. Fok JS, Katelaris CH. Angioedema Masqueraders. *Clin Exp Allergy.* 2019;49(10):1274-1282.
10. Faisant C, Thanh A, Mansard C, Deroux A, Boccon-Gibod I, Bouillet L. Idiopathic non-histaminergic angioedema: successful treatment with omalizumab in five patients. *J Clin Immunol.* 2016; 37(1):80-84.
11. Azofra J, Díaz C, Antépara I, Jaúregui I, Soriano A, Ferrer M. Positive response to omalizumab in patients with acquired idiopathic nonhistaminergic angioedema. *Ann Allergy Asthma Immunol.* 2015;114(5):418-419.e411.
12. Lara-Marquez ML, Christiansen SC, Riedl MA, Herschbach J, Zuraw BL. Threshold-stimulated kallikrein activity distinguishes bradykinin- from histamine-mediated angioedema. *Clin Exp Allergy.* 2018;48(11):1429-1438.