Urticaria unveiled in hereditary angioedema with carboxypeptidase N mutation

To the Editor:

Hereditary angioedema (HAE) is a rare and still poorly known disease that is often overlooked by many health care professionals. The prolonged period between onset of disease attacks and diagnosis heightens the risk of fatalities due to laryngeal angioedema and disease-related morbidity, adversely affecting quality of life for patients and their families alike. Our group has recently proposed the acronym H4AE to underscore the warning signs of HAE, aiming to enhance awareness and facilitate timely diagnosis of this neglected condition (Fig 1). The acronym comprises the initial letters of hereditary angioedema, with 4 *A*'s strategically placed between the *H* and the *E*. HAAAAE (or H4AE) means hereditary, recurrent angioedema, abdominal angioedema/pain, absence of urticaria, absence of response to antihistamines, and estrogen association.[1]

Traditionally, it has been a clinical observation that patients with HAE do not experience urticaria. Although isolated cases of urticaria in patients with HAE have been documented in the literature, these occurrences typically present independently rather than concurrently. Patients generally exhibit a lifetime prevalence of urticaria comparable to that in the general population.[2] Additionally, rash, such as erythema marginatum, is a common prodromal manifestation in patients with HAE and is often misdiagnosed as urticaria.[1-4] Thus, it has now been established that the coexistence of HAE and urticaria, although rare, is plausible. Importantly, hives are not considered a prodromal manifestation or integral to an attack of HAE.

Breaking conventional paradigms, a novel endotype of HAE associated with carboxypeptidase N (CPN) has been elucidated by Vincent et al.[5] This HAE-CPN endotype deviates from previously described types in 2 key respects.

First, patients with HAE-CPN manifest a phenotype marked by episodes of both angioedema and urticaria. CPN plays a pivotal role in cleaving and degrading bradykinin and Lys-bradykinin, as well as the anaphylatoxins C3a and C5a. The mutated CPN compromises its functionality, resulting in reduced bradykinin and anaphylatoxin degradation, potentially triggering both angioedema and urticaria attacks. This challenges the conventional belief that urticaria is not a characteristic feature of HAE, rendering the syndrome more intricate and multifaceted.

Second, unlike most HAE endotypes characterized by increased bradykinin production, HAE-CPN exhibits elevated bradykinin levels owing to impaired degradation by the mutated CPN. This parallels the mechanism observed in acquired angioedema that is induced by drugs such as angiotensin-converting enzyme inhibitors and dipeptidyl peptidase 4 inhibitors.

The discovery of the HAE-CPN endotype adds complexity to our understanding of HAE, emphasizing the need for a thorough approach to diagnosis and treatment. The HAE-CPN endotype challenges conventional perceptions of HAE by revealing a unique phenotype characterized by both angioedema and urticaria.

Ethics approval and data availability: As this is a correspondence, it is exempt from approval by the ethics committee, and all the data contained in it is available in the literature.

DISCLOSURE STATEMENT

The study mentioned in this correspondence was done at the Clinical Immunology and Allergy Division of the University of São Paulo School of Medicine, Brazil, in 2024, using the department's own funding.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Pedro Giavina-Bianchi, MD, PhD
Mara Giavina-Bianchi, MD, PhD
Jorge Kalil, MD, PhD

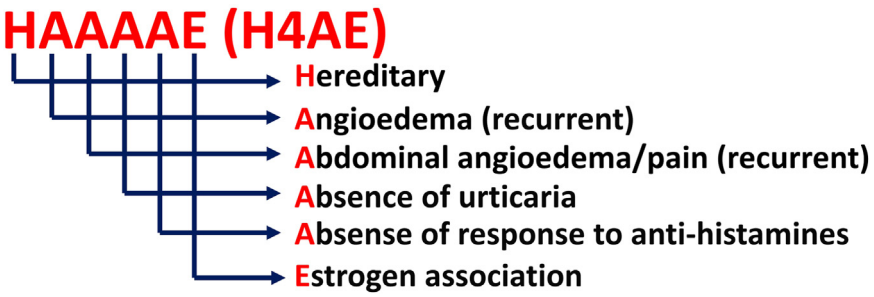

FIG 1. H4AE (HAAAAE): warning signs of HAE.

From the Clinical Immunology and Allergy Division, University of São Paulo School of Medicine, São Paulo, Brazil. E-mail: pbianchi@usp.br.

REFERENCES

1. Giavina-Bianchi P, Aun MV, Garcia JFB, Gomes LS, Ribeiro AJ, Takejima P, et al. Clinical features of hereditary angioedema and warning signs (H4AE) for its identification. Clinics (Sao Paulo) 2022;77:100023.
2. Rasmussen ER, de Freitas PV, Bygum A. Urticaria and prodromal symptoms including erythema marginatum in Danish patients with hereditary angioedema. Acta Derm Venereol 2016;96:373-6.
3. Reshef A, Prematta MJ, Craig TJ. Signs and symptoms preceding acute attacks of hereditary angioedema: results of three recent surveys. Allergy Asthma Proc 2013;34:261-6.
4. Magerl M, Doumoulakis G, Kalkounou I, Weller K, Church MK, Kreuz W, et al. Characterization of prodromal symptoms in a large population of patients with hereditary angio-oedema. Clin Exp Dermatol 2014;39:298-303.
5. Vincent D, Parsopoulou F, Martin K, Gaboriaud C, Demongeot J, Loules G, et al. Hereditary angioedema with normal C1 inhibitor associated with carboxypeptidase N deficiency. J Allergy Clin Immunol Global 2024;3:100223.

https://doi.org/10.1016/j.jacig.2025.100405