Giavina-Bianchi, Aun, Kalil World Allergy Organization Journal (2024) 17:100942
http://doi.org/10.1016/j.waojou.2024.100942

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Vascular endothelial growth factor (VEGF) emerging as a mediator of hereditary angioedema (HAE)

Pedro Giavina-Bianchi, MD, PhD[a]*, Marcelo Vivolo Aun, MD, PhD[a,b] and Jorge Kalil, MD, PhD[a]

To the Editor:

The global standardization of disease definitions and classifications is crucial for effective management, enabling the comparison of case studies and development of successful strategies. A fundamental aspect of precision medicine is tailoring patient care to accommodate their diverse phenotypes and endotypes.

Recently, we proposed refining the classification of recurrent angioedema based on endotypes,[1] as we had previously suggested.[2,3] This refinement would align with the pathophysiological mechanisms responsible for increased vascular permeability.

Recognizing the ongoing advancements in our understanding of hereditary angioedema (HAE), we advocate for an improved classification system based on endotypes, depicted in Fig. 1.[1] This approach offers a rational, practical, and easily applicable framework that aligns with the evolving landscape of angioedema research and clinical practice. The endotype classification of HAE offers a clear structure, encouraging advancements in disease understanding and classification.

Our publication on the endotypes of HAE was a short time ago, but since then, there has been the description of a new mutated gene associated with HAE, the disabled homolog 2 interacting protein (DAB2IP) gene (Fig. 2).[4] The DAB2IP gene encodes a protein involved in several important cellular processes, including the regulation of apoptosis, cell growth, and stress response. The DAB2IP protein acts as a GTPase-activating protein (GAP) that regulates the activity of small GTPases, such as Ras and Rap1, which are crucial for cell signaling. The protein is highly expressed in the vascular endothelium, and can function as an endogenous inhibitor by blocking VEGF receptor 2 (VEGFR2) activity and downstream signaling. Mutations in the DAB2IP gene have been associated with various pathological conditions, including cancer. The mutated DAB2IP protein identified in a family with HAE would have reduced inhibitory action on VEGFR2, resulting in increased vascular permeability due to VEGF action.[4]

Another recent publication regarding HAE was the result of an initiative called DANCE, aimed at better categorizing angioedema syndromes, in which we had the opportunity to participate.[5] The DANCE classification determines 5 subtypes of HAE. Although we congratulate Reshef et al[5] for this project, we believe that some aspects of this classification could be improved. The DANCE classification introduces two new subtypes of angioedema: "vascular endothelium" and "drug-induced," which might not be appropriate. This is because all angioedema subtypes share the common trait of heightened vascular permeability

[a]Clinical Immunology and Allergy Division, University of São Paulo School of Medicine, Brazil
*Corresponding author. Artur Ramos 178 ap.211, Jd. América, São Paulo, SP, CEP:01454-904, Brazil,. E-mail: pbianchi@usp.br
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2024.100942

Received 1 July 2024; Accepted 16 July 2024
Online publication date xxx

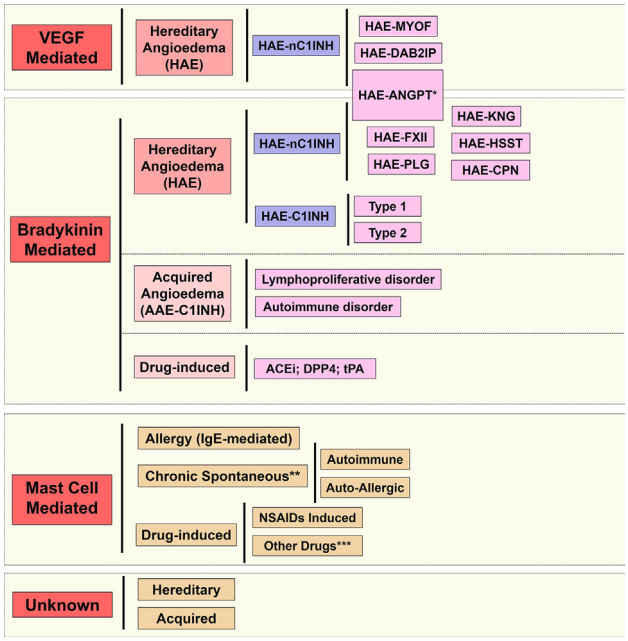

Fig. 1 Endotype classification of recurrent angioedemas. Adapted from: Giavina-Bianchi P et al.[1] The mechanisms proposed in this figure partially represent hypotheses and should be interpreted with caution. While supported by existing scientific evidence, further research is needed to fully validate these findings. * In the figure, HAE-ANGPT is positioned in both the Bradykinin-mediated and VEGF-mediated endotypes because angiopoietin inhibits the actions of both bradykinin and VEGF. ** About 30% of patients experience NSAIDS exacerbated disease. **Other drugs: neuromuscular blocking agents, quinolones, iodine contrast media, opioids, vancomycin, among others. VEGF: vascular endothelial growth factor; HAE: hereditary angioedema; C1INH: C1-inhibitor; HAE-C1INH: HAE due to C1INH deficiency; HAE-nC1INH: HAE with normal C1INH; HAE-ANGPT: HAE due to Angiopoietin 1; HAE-CPN: HAE due to carboxypeptidase N; HAE-DAB2IP: HAE due to disabled homolog 2 interacting protein; HAE-FXII: HAE due to FXII mutation; HAE-HSST: HAE due to Heparan sulfate 3-O-sulfotransferase; HAE-KNG: HAE due to kininogen 1 mutation; HAE-MYOF: HAE due to myoferlin mutation; HAE-PLG: HAE due to plasminogen mutation; AAE-C1INH: acquired angioedema with C1-INH deficiency; ACEi: angiotensin converting enzyme inhibitor; DPP4: dipeptidyl peptidase IV inhibitors; tPA: tissue plasminogen activator.

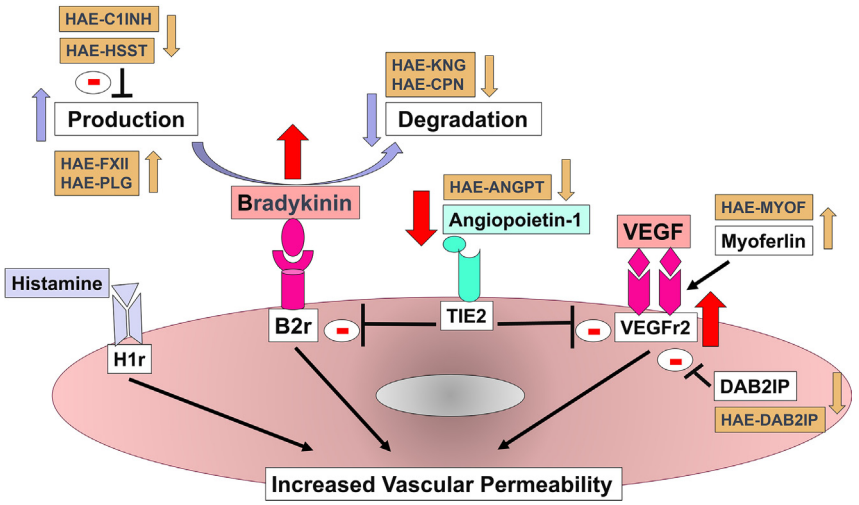

Fig. 2 Pathophysiology of recurrent angioedema with its endotypes and mediators. Adapted from: Giavina-Bianchi P et al.[1] The mechanisms proposed in this figure partially represent hypotheses and should be interpreted with caution. While supported by existing scientific evidence, further research is needed to fully validate these findings. The figure illustrates the pathophysiology of HAE-C1INH and HAE-nC1INH with its 8 endotypes. The two mediators that have a direct effect on increasing vascular permeability in hereditary angioedema are bradykinin and VEGF. A third mediator, angiopoietin, has an inhibitory effect on the first two. The red arrow pointing upwards represents an increase in function, while the red arrow pointing downwards represents a decrease. The mutated genes are in orange boxes. The orange arrows pointing upwards represent gain-of-function mutations, while the arrows pointing downwards represent loss-of-function mutations. The minus symbol inside the white circles represents inhibitory action. B2r: bradykinin receptor B2; VEGF: vascular endothelial growth factor; VEGFr2: VEGF receptor 2; TIE2: tunica interna endothelial cell kinase 2; H1r: histamine receptor H1; HAE-C1INH: HAE due to C1INH deficiency; HAE-nC1INH: HAE with normal C1INH; HAE-ANGPT: HAE due to Angiopoietin 1; HAE-CPN: HAE due to carboxypeptidase N; HAE-DAB2IP: HAE due to disabled homolog 2 interacting protein; HAE-FXII: HAE due to FXII mutation; HAE-HSST: HAE due to Heparan sulfate 3-O-sulfotransferase; HAE-KNG: HAE due to kininogen 1 mutation; HAE-MYOF: HAE due to myoferlin mutation; HAE-PLG: HAE due to plasminogen mutation.

due to specific mediator actions, and the denomination of 1 HAE subtype as "vascular endothelium" can be misinterpreted. Additionally, there is's an oversight in the classification of drug-induced angioedema, as it does not differentiate whether the causative drug acts by increasing bradykinin or activating mast cells. A classification of drug-induced angioedema based on endotypes can help clinicians select appropriate treatments. Attacks induced by nonsteroidal anti-inflammatory drugs usually respond to antihistamines, whereas bradykinin-mediated angioedema, caused by drugs such as angiotensin-converting enzyme inhibitors, tends to be refractory to this treatment and may require the use of icatibant.

In conclusion, we emphasize the necessity of a precise and dynamic classification system for HAE that evolves with our growing understanding of the disease. By adopting an endotype-based classification, we can more accurately reflect the underlying pathophysiological mechanisms, facilitating better patient care and more targeted treatments. The discovery of the DAB2IP gene mutation's association with HAE highlights the ongoing advancements and the need for continual refinement of classification systems. A well-defined endotype framework not only aids in the clinical management of HAE but also promotes research that could lead to novel therapeutic strategies, ultimately improving patient outcomes.

Abbreviations
DAB2IP; Disabled homolog 2 interacting protein, GAP; GTPase-activating protein, HAE; Hereditary Angioedema, VEGF; Vascular Endothelial Growth Factor, VEGFr2; VEGF receptor 2.

Funding
Not applicable.

Availability of data and materials
It does not apply.

Author contributions
All authors participated in the design and the development of the present letter.

Ethics statements
As this work is a correspondence, it is exempt from approval by the ethics committee.

Consent for publication
All authors wrote, read, approved, and consented to the publication of this manuscript.

Declaration of competing interest
The authors have no financial or conflicts of interest to disclosure.

Acknowledgments
To the physicians Ana Júlia Ribeiro, Mara Giavina-Bianchi, Rosana Camara Agondi, and Antônio Abílio Motta, who provide assistance with us to patients with HAE, and who help us generate knowledge about the disease. We thank Pablo Martinez, MSc, and Mariana Paes Leme Ferriani, MD, PhD, for their suggestions, which significantly enhanced the quality of the figures in this paper.

Author detail
[a]Clinical Immunology and Allergy Division, University of São Paulo School of Medicine, Brazil [b]Hospital Israelita Albert Einstein, Faculdade Israelita de Ciências da Saúde Albert Einstein, Brazil.

REFERENCES

1. Giavina-Bianchi P, Aun MV, Giavina-Bianchi M, et al. Hereditary angioedema classification: expanding knowledge by genotyping and endotyping. *World Allergy Organ J*. 2024;17(5):100906.
2. Giavina-Bianchi P, Aun MV, Motta AA, Kalil J, Castells M. Classification of angioedema by endotypes. *Clin Exp Allergy*. 2015;45(6):1142–1143.
3. Giavina-Bianchi P, Aun MV, Jares EJ, Kalil J. Angioedema associated with nonsteroidal anti-inflammatory drugs. *Curr Opin Allergy Clin Immunol*. 2016;16(4):323–332.
4. D'Apolito M, Santacroce R, Vazquez DO, et al. DAB2IP associates with hereditary angioedema: insights into the role of VEGF signaling in HAE pathophysiology. *J Allergy Clin Immunol*. 2024;S0091-6749(24):558. X.
5. Reshef A, Buttgereit T, Betschel SD, et al. The definition, acronyms, nomenclature, and classification of angioedema: AAAAI, ACAAI, ACARE, and APAACI DANCE consensus. *J Allergy Clin Immunol*. 2024:S0091-6749(24)00407-X.