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REVIEW

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Hereditary angioedema classification: Expanding knowledge by genotyping and endotyping

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ABSTRACT

Hereditary angioedema (HAE) encompasses a group of diseases characterized by recurrent, genetically mediated angioedema associated with increased vascular permeability primarily due to bradykinin. The disease poses diagnostic challenges, leading to underdiagnosis and delayed therapy. Severe manifestations include laryngeal and intestinal angioedema, contributing to significant morbidity and mortality. If left undiagnosed, the estimated mortality rate of the disease ranges from 25% to 40% due to asphyxiation caused by laryngeal angioedema. There is a pressing need to enhance awareness of hereditary angioedema and its warning signs. The acronym "H4AE" may facilitate the memorization of these signs. This study comprehensively reviews clinical, laboratory, and physiopathological features of documented HAE subtypes. The study advocates for an improved HAE classification based on endotypes, building on the knowledge of angioedema pathophysiology. The proposed endotype classification of HAE offers a clear and applicable framework, encouraging advancements in disease understanding and classification.

Keywords: Hereditary angioedema, C1 inhibitor deficiency, Classification, Endotype, Phenotype, Disease awareness, H4AE, Bradykinin, Vascular permeability, Angioedema pathophysiology, Genetic mutations, Laryngeal angioedema, Intestinal angioedema, Morbidity and mortality

INTRODUCTION

Angioedema is a localized, self-limiting, asymmetric, and disfiguring non-inflammatory edema of the subcutaneous and submucosal tissues that occurs as a result of increased vascular permeability. Hereditary angioedema (HAE) comprises a group of diseases characterized by recurrent angioedema associated with a genetic mutation passed down through subsequent generations and primarily mediated by bradykinin.[1–3]

HAE is a rare and still unknown disease, which is underdiagnosed by many health professionals. The long time elapsed between the onset of disease attacks and the diagnosis, as well as the access to therapy, increases the risk of death from laryngeal angioedema and disease-related morbidity,

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affecting the quality of life of patients and their families.[4–9] Recently, our group suggested the acronym "H4AE" to remind of the warning signs of HAE, which may be useful in raising awareness and improving the diagnosis of this neglected disease (Fig. 1).[8] The acronym includes the initials of Hereditary Angioedema (HAE), with four "As" inserted between the "H" and the "E." "HAAAAE or H4AE" represents Hereditary, recurrent Angioedema, Abdominal pain, Absence of urticaria, Absence of response to antihistamines, and Estrogen association.

The 2 most severe clinical manifestations of HAE are related to laryngeal and intestinal angioedema. If left undiagnosed, the estimated mortality rate of the disease ranges from 25% to 40% due to asphyxiation caused by laryngeal angioedema. Incapacitating intestinal angioedema is another major manifestation of HAE, and many patients undergo abdominal surgery by mistake.[5,6,8,9] A recent Brazilian study identified 39 deaths due to asphyxiation from laryngeal angioedema in 46 families of 170 patients with HAE. Of the deceased patients, 87.2% had no previous diagnosis of HAE. Forty-one percent of the deaths occurred outside the hospital, with more than 8 h elapsing after the onset of the HAE attack in half of the patients.[10]

The objective of our study is to comprehensively review the clinical and laboratory features, along with the physiopathology, of all the subtypes of Hereditary Angioedema (HAE) that have been documented. Additionally, we aim to improve the classification of HAE based on its endotypes.

METHODS

The present study is a narrative review of the literature, critically analyzing all identified subtypes of HAE and current disease classifications. The review included searches of PubMed, Web of Science, Embase and Lilacs from inception to December 2023. Additionally, manual searches of study references and review articles were conducted. The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and keywords: "Hereditary Angioedema AND case series"; "Hereditary Angioedema AND clinical case studies"; "Hereditary Angioedema AND Classification"; "Hereditary Angioedema AND Endotype"; "Hereditary Angioedema AND C1 Inhibitor"; "Hereditary Angioedema AND Factor XII"; "Hereditary Angioedema AND Plasminogen"; "Hereditary Angioedema AND Angiopoietin-1"; "Hereditary Angioedema AND Kininogen-1"; "Hereditary Angioedema AND Myoferlin"; "Hereditary Angioedema AND Heparan sulfate 3-O-sulfotransferase"; and "Hereditary Angioedema AND Carboxypeptidase N". This comprehensive review encompasses the original descriptions of each HAE subtype, case series, clinical case studies, as well as both the original and updated disease guidelines.[1–3,11–14] The search was limited to articles published in English, Spanish, or Portuguese. We conducted a thorough and critical evaluation of all studies aiming to describe and classify HAE, with a particular emphasis on classifications utilizing an endotype-based approach.

RESULTS AND DISCUSSION

In the PubMed platform, our search strategy identified: 36 manuscripts for "Hereditary Angioedema AND case series"; 74 for "Hereditary Angioedema AND clinical case studies"; 119 for "Hereditary Angioedema AND Classification"; 6 for "Hereditary Angioedema AND Endotype"; 2146 for "Hereditary Angioedema AND C1 Inhibitor"; 259 for "Hereditary Angioedema AND Factor XII";

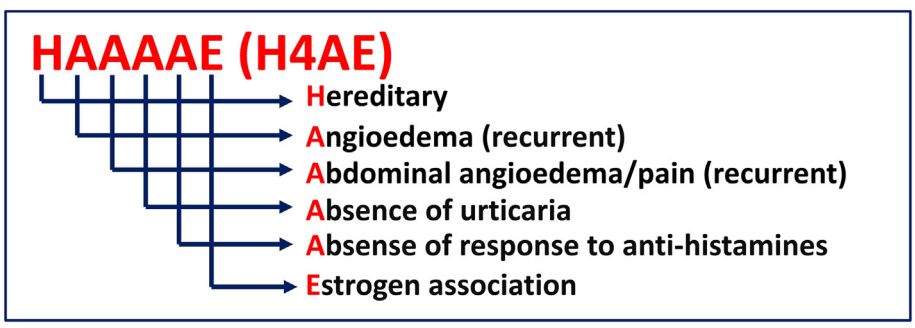

Fig. 1 "H4AE" (HAAAAE): Warning signs of Hereditary Angioedema

103 for "Hereditary Angioedema AND Plasminogen"; 26 for "Hereditary Angioedema AND Angiopoietin-1"; 70 for "Hereditary Angioedema AND Kininogen-1"; 11 for "Hereditary Angioedema AND Myoferlin"; 4 for "Hereditary Angioedema AND Heparan sulfate 3-O-sulfotransferase"; and 7 for "Hereditary Angioedema AND Carboxypeptidase N".

Quincke first described HAE as a clinical entity in 1882,[15] and Osler established its hereditary nature in 1888.[16] The biochemical defect that induces the disease, C1 inhibitor (C1–INH) deficiency, was not identified until 75 years later.[17] Patients with HAE due to C1–INH deficiency (HAE-C1INH; OMIM #106100) present with a quantitative or qualitative defect of this protein. C1–INH is a serine protease inhibitor from the SERPIN superfamily, which inhibits the first components of the complement system-classical pathway, C1r and C1s esterases, preventing their binding to and activation of C1q. In the absence of such inhibition, the complement system becomes excessively activated, leading to a decrease of C4 levels.[18,19] C1–INH has also been recognized as an inhibitor of several proteases, including plasma kallikrein, coagulation factors XII (FXII) and XI, plasmin and MASP-1 and MASP 2, which are components of the complement system-lectin pathway. Therefore, C1–INH not only inhibits the complement system but also plays a crucial role in regulating the contact, coagulation, and fibrinolysis systems.[20]

In 1999, Nussberger et al assessed plasma samples from patients with HAE, noting elevated bradykinin levels in blood drawn from edematous sites compared to unaffected sites.[21] Subsequent to this, an experimental study provided crucial insights by demonstrating lower vascular permeability in double knockout mice with concurrent deficiencies in bradykinin receptor B2 (BDKRB2) and C1 inhibitor (C1–INH) compared to mice with only C1–INH deficiency. This emphasized the pivotal role of the bradykinin/BDKRB2 pathway in angioedema.[22] Today, it is firmly established that bradykinin is the main mediator of HAE. The emergence of innovative treatments, such as bradykinin receptor antagonists and kallikrein inhibitors, has further solidified the recognition of bradykinin as the primary mediator in HAE-C1INH.[23,24]

Over the last 5 decades, case series have been published describing the clinical and laboratory characteristics, as well as the management, of patients with HAE. These comprehensive clinical case studies serve as poignant illustrations, revealing the challenges in promptly identifying the disease, the consequent delays in diagnosis, and the substantial morbidity and mortality risks intricately connected to this condition (Table 1).[4–6,8,9]

In 2000, Bork et al described a novel subset of patients with HAE exhibiting normal C1–INH levels and function (HAE-nC1INH).[25] At that time, this HAE type was designated HAE type III. Subsequently, their research group identified mutations in the gene encoding coagulation factor XII (FXII) in some families of patients with HAE and normal C1–INH levels (HAE-FXII).[26,27] FXII plays a pivotal role in the early stages of contact system activation, participating in both thrombosis and inflammation, ultimately leading to increased brady kinin synthesis.[28]

Scientific evidence suggests that mutations in FXII result in gain-of-function changes, leading to subsequent increases in bradykinin production. Studies involving recombinant natural and mutated variants of FXII have demonstrated that FXII-HAE mutations introduce new sites sensitive to enzymatic cleavage by plasmin, rendering FXII mutants abnormally responsive to plasmin. The FXII mutants rapidly activate after cleavage by plasmin, evading inhibition through C1–INH, resulting in excessive bradykinin production.[27,29] Lysine analogs, including tranexamic acid and epsilon aminocaproic acid, may mitigate these changes, elucidating the therapeutic value of these agents in patients with FXII-HAE.[29]

Since the initial description of FXII-HAE,[26,27] 6 additional genetic mutations associated with normal C1–INH have been identified: plasminogen (HAE-PLG),[30] angiopoietin 1 (HAE-ANGPT),[31] kininogen 1 (HAE-KNG),[32] myoferlin (HAE-MYOF),[33] heparan sulfate 3-O-sulfotransferase (HAE-HSST),[34] and carboxypeptidase N (HAE-CPN).[35] In relation to the pathophysiology of HAE-nC1INH, we observe an increase in bradykinin concentration and, consequently, its action in almost all endotypes of this syndrome. The exception would be the endotypes of HAE-nC1INH associated with mutations in angiopoietin 1 and

Case Series	Agostoni A & Cicardi M (1992)[5]	Bork K et al. (2006)[6]	Giavina-Bianchi P et al. (2022)[8]	Christiansen SC et al. (2023)[9]
n patients (n of families)	226 (80)	221 (108)	98 (–)	485 (–)[a]
Attacks onset (y.o.)	–	11.2 (mean)	12.7 (mean)	12.0 (median)
Percentage of the patients <20 y.o. at attacks onset	85%	84.2%	–	–
Delay to diagnosis	–	–	13.7 y (mean)	5 y (median)
Without family history	8.0%	9.5%	24.7%	24.0%
n of attacks	46% of the patients >5/y	–	11.3/y (mean)	34.3% of the patients >2/m
Rate of assimptomatic patients	–	5.4%	–	–
Subcutaneous Attacks	91%	100%	97.5%	Often
Abdominal Attacks	73%	97%	87.6%	Often
Laryngeal Attacks	48%	54%	46.9%	Rarely
Tracheostomy or Tracheal Intubation	9.3%	–	21.3%	16%
Abdominal Surgery	–	–	26.9%	16%
On long-term prophylaxis	38.1%	–	70.4%	57.3%

Table 1. Case Series of Hereditary Angioedema with C1-INH deficiency (HAE-C1INH): Clinical and Treatment Features *–: data missing; n: number; y.o.: years old; y: years; m: month. [a]Register with information from patients*

myoferlin proteins. In the case of angiopoietin 1, the mutated protein has lower affinity for its receptor, reducing its inhibitory action on bradykinin and vascular endothelial growth factor, another mediator that induces increased vascular permeability.[31] Regarding myoferlin, it is hypothesized that the mutated protein may lead to an increase in the expression of vascular endothelial growth factor receptors on the endothelial surface, potentially resulting in an increase in the mediator's action (Fig. 2).[33]

The HAE-CPN endotype, more recently described, differs from previously described ones, as patients exhibit a phenotype characterized by crises of both angioedema and urticaria. Carboxypeptidase N cleaves and degrades bradykinin and lys-bradykinin, as well as the anaphylatoxins C3a and C5a. The mutated protein would have its action compromised, decreasing bradykinin and anaphylatoxin degradation, which could lead to angioedema and urticaria attacks.[35] This renders the syndrome more intriguing and complex, as the absence of urticaria was considered a characteristic of HAE. Table 2. A provides details on the gene mutation, endotype classification, proposed pathophysiology, and inheritance pattern for the seven subtypes of HAE with normal C1–INH. Table 2.B outlines the clinical features of each subtype and proposes treatment options for them.

The mechanisms proposed in this table partially represent hypotheses and should be interpreted with caution. While supported by existing scientific evidence, further research is needed to fully validate these findings.

Professor William Osler's insightful assertion that "Medicine is both a science and an art" reverberates through the ever-evolving landscape of disease understanding and classification. At the core of medical science lies the essential practice of thorough analysis and categorization of diseases, a process driven by scientific evidence. However, the genuine artistry of medicine comes to life in the personalized care of individuals, where the prioritization of their unique biopsychosocial and spiritual features becomes paramount. This blending of scientific rigor with participative and individualized patient care encapsulates the true essence of the medical profession, reflecting its dual nature as both a science and an art.

In 2015, our group proposed a classification of recurrent angioedema based on endotypes. This classification was based on the two major pathophysiological mechanisms of angioedema that had been described: one induced by the activation of

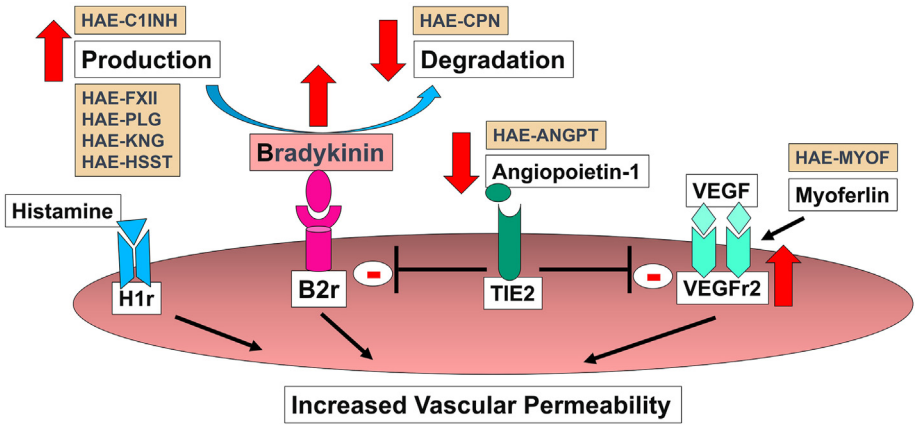

Fig. 2 Pathophysiology of recurrent angioedema with its endotypes and mediators. The mechanisms proposed in this figure partially represent hypotheses and should be interpreted with caution. While supported by existing scientific evidence, further research is needed to fully validate these findings. The figure illustrates the pathophysiology of HAE-C1INH and HAE-nC1INH with its seven endotypes. 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-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

Nomenclature	Gene Mutation	Endotype	Pathophysiology	Inheritance pattern
HAE-FXII	Factor XII Chromosome 5 (OMIM #610618)	Increase production of Bradykinin.	FXII abnormally sensitive to plasmin	1:400,000 Autosomal dominant trait.
HAE-PLG	Plasminogen Chromosome 6	Increased production of Bradykinin.	Increased plasminogen activity with increased plasmin formation.	Autosomal dominant trait.
HAE-ANGPT	Angiopoietin 1 Chromosome 8	Increased action of Bradykinin.	Mutation of the angiopoietin-1 gene leads to changes in the protein, reducing its interaction with its receptor and its inhibitory action on bradykinin.	Autosomal dominant trait.
HAE-KNG	Kininogen 1 Chromosome 3	Increased production of Bradykinin.	Altered high- and low-molecular-weight kininogens are more prone to be cleaved by kallikrein, and/or generate bradykinin with increased activity.	Autosomal dominant trait.
HAE-MYOF	Myoferlin Chromosome 10	Increased action of vascular endothelial growth factor (VEGF)	Myoferlin increases VEGFR-2 expression and VEGF action.	Autosomal dominant trait.
HAE-HSST	Heparan sulfate–glucosamine 3-O-sulfotransferase 6 Chromosome 16	Increased production of Bradykinin.	The mutation of the protein reduces the stabilization of high molecular weight kininogen at the level of the cell membrane, which is cleaved, releasing bradykinin.	Autosomal dominant trait.
HAE-CPN	Carboxypeptidase N	Decrease degradation of Bradykinin.	Reduced cleavage and inactivation of bradykinin and lys-bradykinin, as well as of the anaphylatoxins C3a and C5a, resulting in angioedema and urticaria.	Autosomal dominant trait.

Table 2.A. HAE with normal-C1-INH: gene mutation, endotype classification, proposed pathophysiology, and inheritance pattern

Nomenclature	n of families (n of symptomatic patients)	Clinical features	Proposed treatment	Author (date)
HAE-FXII	185 (446)	Female predominance (1:10). Triggering and worsening with estrogens. Mean age at disease onset (y): around 20 (range 1–65). No erythema marginatum. Tongue and laryngeal angioedema. Bruising or ecchymosis at the site of skin angioedema. Fatal cases.	Discontinuation of estrogen-containing drugs and ACEi. Icatibant for attacks. Plasma-derived C1-INH (pd-C1-INH) concentrate for attacks, short-term and long-term prophylaxis. Progestins, tranexamic acid, and attenuated androgens for long-term prophylaxis.	Dewald G, Bork K (2006)[26] Cichon S (2006)[27] Bork K (2020)[36]
HAE-PLG	33 (146)	Female predominance. No worsening during pregnancy. Mean age at disease onset (y): 30.5 (SD 15.5; range 5–72). No erythema marginatum. Tongue angioedema. Intubation and cricothyrotomia. Fatal cases.	Icatibant for attacks. pd-C1-INH concentrate was irregularly effective for attacks. Tranexamic acid for long-term prophylaxis.	Bork K (2018)[30] Bork K (2020)[36]
HAE-ANGPT	1 (4)	Disease onset in the second decade. Abdominal angioedema with unnecessary surgery,	Tranexamic acid for long-term prophylaxis.	Bafunno V (2018)[31]
HAE-KNG	1 (6)	Mean age at disease onset (y): 35 (SD 16.2; range 17–55). Triggering and worsening with estrogens and pregnancy. Tongue and abdominal angioedema.	pd-C1-INH concentrate was effective for attacks.	Bork K (2019)[32]

(continued)

Nomenclature	n of families (n of symptomatic patients)	Clinical features	Proposed treatment	Author (date)
HAE-MYOF	1 (3)	Disease onset in the second decade. Female predominance and worsening during menstruation.	–	Ariano A (2020)[33]
HAE-HSST	1 (4)	Disease onset in the second decade. Female predominance and worsening with estrogens. Tongue, laryngeal and abdominal angioedema, with diarrhea. Spontaneous abortion.	–	Bork K (2021)[34]
HAE-CPN	4 (14)	Female predominance and worsening with estrogens. Laryngeal and Abdominal angioedema. Patients exhibit a distinct phenotype, as it encompasses **URTICARIA**.	Icatibant for attacks. Tranexamic acid for long-term prophylaxis. Montelukast is also used.	Vincent D (2024)[35]

Table 2.B. (Continued) HAE with normal-C1-INH: clinical features and proposed treatment

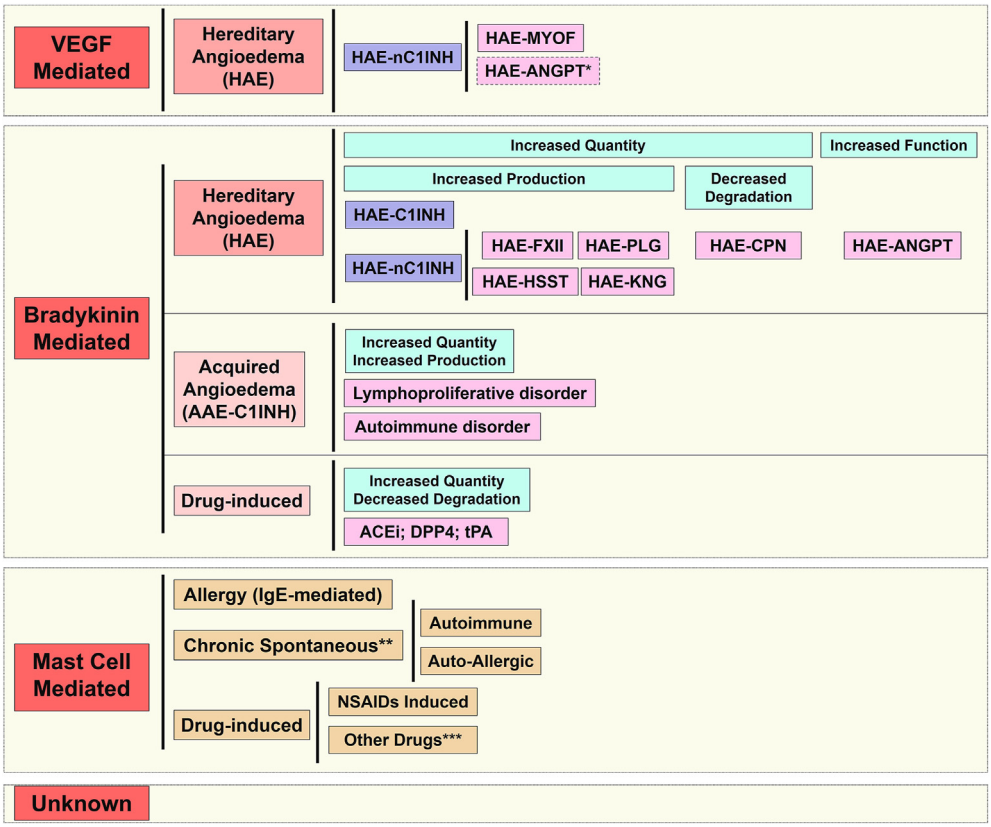

Fig. 3 Endotype Classification of Recurrent Angioedemas. The mechanisms proposed in this figure partially represent hypotheses and should be interpreted with caution. While supported by existing scientific evidence, further research is needed to fully validate these findings. * In the figure, HAE-ANGPT 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-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

mast cells and basophils, resulting in release of histamine and other mediators (histaminergic angioedema), and the other mediated by bradykinin (bradykinin-mediated or non-histaminergic angioedema), as seen in hereditary angioedema, acquired angioedema with C1–INH deficiency (lymphoproliferative and autoimmune disorders) and in angioedema induced by drugs such as angiotensin-converting enzyme inhibitors and DPP-4 inhibitors.[37,38] However, the growing knowledge in the area calls for and justifies an improvement in the current classifications of recurrent angioedema, but maintaining the classification based on endotypes. This approach involves a division grounded in the pathophysiological mechanism responsible for the increase in vascular perme-ability.

Recognizing the ongoing advancements in our understanding of HAE, we advocate for an improved classification system based on endotypes. This approach, depicted in Fig. 3, offers a rational, practical, and easily applicable framework that aligns with the evolving landscape of angioedema research and clinical practice.

CONCLUSION

There is a pressing need to enhance awareness of hereditary angioedema and its warning signs. The acronym H4AE may facilitate the memo-rization of these signs. The proposed endotype classification of HAE offers a clear and applicable framework, encouraging advancements in disease understanding and classification.

Abbreviations

AAE-C1INH, acquired angioedema with C1–INH deficiency; C1–INH, C1 inhibitor; FXII, coagulation factor XII; HAE, Hereditary angioedema; H4AE, acronym represents Hereditary, recurrent Angioedema, Abdominal pain, Absence of urticaria, Absence of response to antihistamines, and Estrogen association; 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-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; VEGF, vascular endothelial growth factor.

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Authors' contributions

All authors participated in the design and the development of the present study.

Ethical approval

As the study is a review, it is exempt from approval by the ethics committee, and all the data contained in it is available in the literature.

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.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Chat GPT in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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