REVIEW ARTICLE

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Hereditary Angioedema

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Hereditary angioedema is a rare, potentially life-threatening disorder characterized by attacks of cutaneous and submucosal swelling. Quincke first described its clinical presentation, and Osler's recognition of the autosomal dominant inheritance pattern followed in 1888.[1] The initial name of the disorder, "hereditary angioneurotic edema," conveyed the bias that it devolved from neurosis. Over the past 40 years, scientific investigations have identified the fundamental defect of hereditary angioedema as a deficiency of functional C1 inhibitor protein, a protease inhibitor in the serpin superfamily,[2,3] and have established that bradykinin is the biologic mediator of swelling.[4,5] In 2000, hereditary angioedema with normal C1 inhibitor levels was described, for which molecular mechanisms are emerging.[6,7] Despite progress in unraveling the pathophysiology of hereditary angioedema, a delay in proper diagnosis and a paucity of effective therapeutic approaches have hampered effective management of the disease until recently. Advances envisioned in 2008,[8] however, have now been realized, with insights from basic research translated into novel therapies.

This article reviews the progress made during the past decade in elucidating the pathophysiological mechanisms of hereditary angioedema and the subsequent development of targeted treatments for the disorder, with anticipated reductions in morbidity and mortality and an improved quality of life. The clinical vignette below illustrates the profound effect of these treatments.

CLINICAL CASE

A 26-year-old woman presented with a history, since early childhood, of skin swelling, severe abdominal pain, nausea, and vomiting. Attacks occurred nearly weekly, resolving spontaneously over a period of 2 to 5 days. Laryngeal swelling required intubation on four occasions. The episodes were largely unpredictable. The patient's mother and brother had similar but less frequent and milder attacks. At 8 years of age, the patient received a diagnosis of hereditary angioedema (C4 level, 0.06 g per liter [normal range, 0.10 to 0.40]; C1 inhibitor antigen level, 0.06 g per liter [normal range, 0.21 to 0.39]; and C1 inhibitor function, 14% [normal range, >40%]). Early treatment relied on up to 400 mg daily of danazol, an attenuated androgen, with sequelae of obesity, virilization, and increased hepatic enzyme levels. Management of acute attacks was limited to pain medication and intravenous fluids for abdominal attacks and fresh-frozen plasma for laryngeal swelling. Cutaneous angioedema was untreated. The patient had anxiety and depression, as well as multiple limitations such as an inability to exercise, many missed days of school, and a constrained social life.

Shortly after it was approved by the Food and Drug Administration (FDA), plasma-derived C1 inhibitor (Cinryze, Takeda) was initiated prophylactically, at a dose of 1000 units administered twice weekly at an infusion center. Treatment of

acute symptoms included plasma-derived C1 inhibitor and, after FDA approval, icatibant, a bradykinin B2 receptor inhibitor. Breakthrough attacks continued; infusions were increased to three times a week, with marginal improvement. The patient began to administer plasma-derived C1 inhibitor herself, but she had difficulty with venous access, and placement of an indwelling port was required.

The patient entered a clinical trial of subcutaneous lanadelumab (a monoclonal antibody to plasma kallikrein) and continued in the open-label extension study until FDA approval in 2018. She has had only two mild attacks since initiation of this therapy. The effect on her quality of life has been dramatic. She began an exercise and diet program, losing more than 45 kg. Her mood improved. She completed college and began working and enjoying international travel and personal relationships.

PATHOPHYSIOLOGY AND MECHANISMS OF HEREDITARY ANGIOEDEMA

Angioedema is the physical manifestation of transient increases in vascular permeability. Bradykinin, generated by activation of the plasma contact system, has been conclusively identified as the mediator of swelling in hereditary angioedema with C1 inhibitor deficiency.[1,4,8,9] The plasma contact system comprises coagulation factor XII, plasma prekallikrein, and high-molecular-weight kininogen; plasma prekallikrein and high-molecular-weight kininogen circulate as a 1:1 bimolecular complex.[10,11] In vivo, the components assemble on the surface of endothelial cells in a zinc-dependent manner (Fig. 1). Despite the interactions between the activated plasma contact and fibrinolytic systems, patients with hereditary angioedema do not appear to be at an increased risk for bleeding or thrombosis.[16,17]

The fundamental abnormality in hereditary angioedema types I and II is a deficiency of functional C1 inhibitor (due to a mutation in *SERPING1*), which regulates multiple proteases involved in the complement, contact-system, coagulation, and fibrinolytic pathways. Within the contact cascade, C1 inhibitor inactivates plasma kallikrein, factor XIIa, and factor XIIf, operating as a "molecular mousetrap." When the Arg444–Thr445 bond in the reactive loop of the molecule is cleaved, a conformational rearrangement is triggered — called suicide inactivation — that irreversibly buries the protease in the C1 inhibitor molecule. Suicide inactivation results in a thermodynamically stable C1 inhibitor–protease complex.

The mutations that lead to hereditary angioedema type I are diverse, with missense, nonsense, frameshift deletion or insertion, or splicing defects scattered throughout the gene, resulting in truncated or misfolded C1 inhibitor that is not efficiently secreted.[18,19] In hereditary angioedema type II, the defect is typically a missense mutation in exon 8,[20] affecting the mobile loop and interfering with the ability to inhibit target proteases, with rare exceptions.[21] The critical functional threshold for C1 inhibitor control of the plasma contact system is approximately 40%.[22] Functional C1 inhibitor levels in hereditary angioedema with C1 inhibitor deficiency are generally 5 to 30% of the normal level, despite the presence of one normal gene. The cause of this discrepancy has been proposed to involve enhanced clearance of C1 inhibitor–protease complexes, cleavage of C1 inhibitor into an inactive, 94-kD form, and inhibition of the normal gene product by the abnormal one, designated as "transinhibition."[9] A dominant negative effect on C1 inhibitor protein secretion has also been reported.[23]

In hereditary angioedema with C1 inhibitor deficiency, activation of the plasma contact system generates bradykinin, which transduces its biologic effect through the engagement of G protein–coupled receptors. The bradykinin B2 receptor is constitutively expressed on endothelial cells and is considered to be principally responsible for the active transfer of fluid into localized tissues, with resultant angioedema. Mechanistically, activation of the bradykinin B2 receptor results in dissolution of the adherens junction, which plays a critical role in limiting vascular permeability (Fig. 1). After bradykinin B2 receptor engagement, downstream signaling phosphorylates the transmembrane vascular endothelial cadherin molecules, which are then internalized and degraded. The ensuing actin cytoskeleton contraction increases pore sizes between endothelial cells, with consequent vascular leakage.[9] In addition to the bradykinin B2

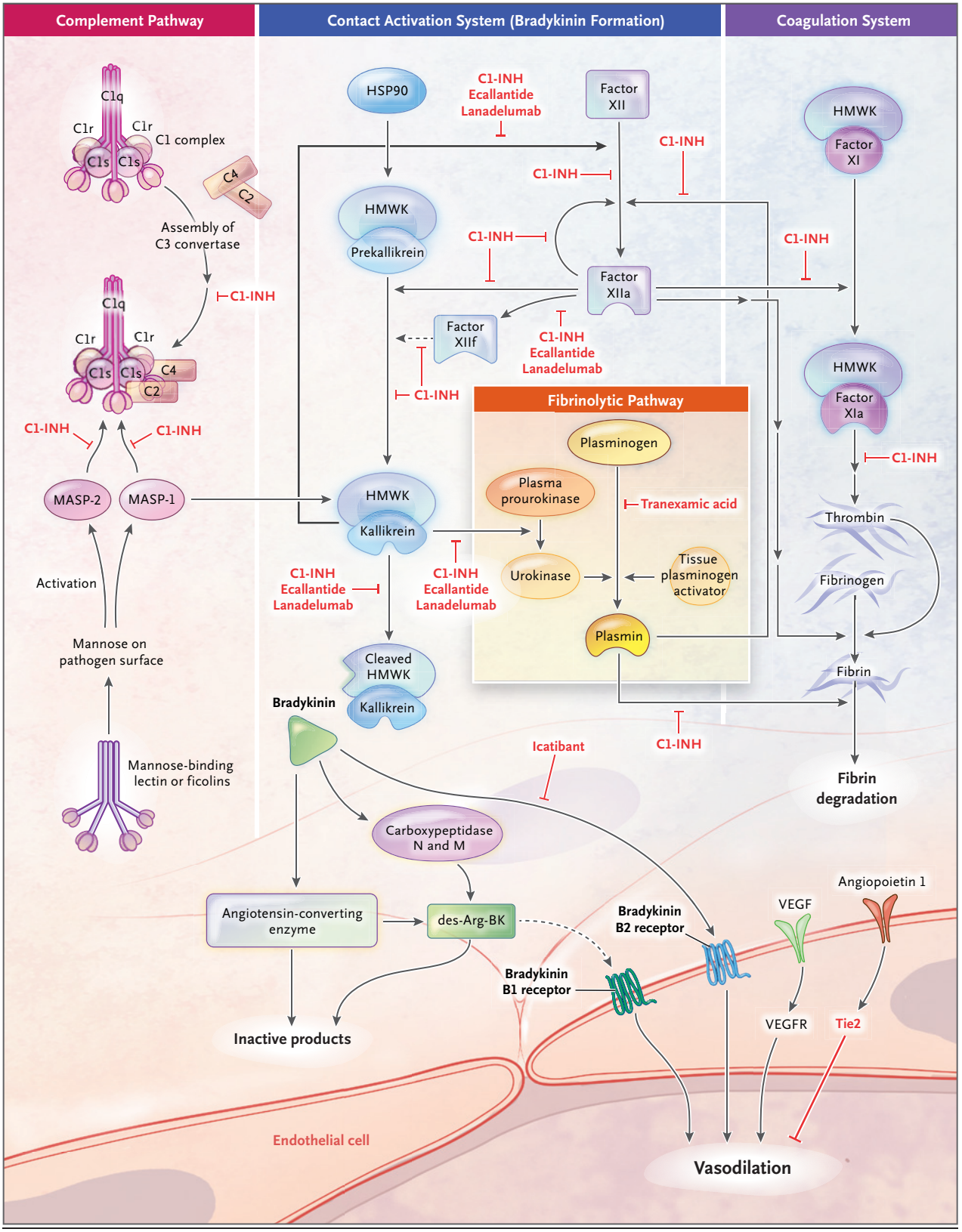

Figure 1 (facing page). Contact, Complement, and Fibrinolytic Systems in Hereditary Angioedema (HAE) and Targets for Available Therapy.

The plasma contact system consists of coagulation factor XII, plasma prekallikrein, and high-molecular-weight kininogen (HMWK). Also shown are mechanisms of action for drugs that are currently approved for the treatment of HAE with C1 inhibitor (C1-INH) deficiency; sites of inhibition by C1-INH, ecallantide, lanadelumab, and icatibant in the plasma contact system activation cascade are shown in red. Coagulation factor XII and the prekallikrein–HMWK complex have weak intrinsic enzymatic activity; an absence of C1-INH produces their active forms, factor XIIa and plasma kallikrein, respectively. Autoactivation, kallikrein, and plasmin produce additional factor XIIa. Factor XII fragment (factor XIIf) weakly stimulates the prekallikrein–HMWK complex to produce the kallikrein–HMWK complex (black dashed arrow). Without sufficient levels of functional C1-INH to inhibit plasma kallikrein, HMWK is cleaved, producing bradykinin. Cleaved HMWK may be a biomarker of disease activity.[12] Heat shock protein 90 (HSP90), which is constitutively secreted by endothelial cells,[12] also activates the prekallikrein–HMWK complex. C1-INH regulates the lectin pathway. Levels of mannose-binding lectin–associated serine protease 1 (MASP-1), MASP-1–C1-INH, and ficolin-3 may correlate with HAE activity; further validation is required.[13,14] Factor XII–independent activation of HMWK cleavage occurs through HSP90 and potentially through MASP-1.[11] Bradykinin, generated through the plasma contact system, binds to the bradykinin B2 receptor on endothelial cells. Bradykinin B2 receptor activation produces angioedema (fluid transfer) through several mechanisms, including increased endothelial-cell permeability, enhanced phosphorylation and inactivation of vascular endothelial cadherin, and expression of vascular permeability factors (vascular endothelial growth factor [VEGF]), all of which create vascular pores. Endothelial-cell activation promotes vasodilation and increased plasma osmolality.[9,11,15] Induction and activation of bradykinin B1 receptor through inflammation and through engagement of bradykinin B2 receptor may be involved in angioedema.[9,11] Bradykinin (BK) that is unbound and Lys-BK (not shown) are rapidly inactivated by angiotensin-converting enzyme and carboxypeptidases N and M to des-Arg-BK and des-Arg-Lys-BK (not shown), respectively. Des-Arg-BK is a weak ligand for bradykinin B1 receptor (indicated by the gray dashed arrow) and is of uncertain importance in HAE. Tissue kallikrein cleaves low-molecular-weight kininogen, releasing Lys-BK, which is acted on by carboxypeptidase, generating des-Arg-Lys-BK, a potent ligand for bradykinin B1 receptor (not shown). There is no evidence that the tissue kallikrein system is activated in HAE. Mutations in angiopoietin-1 prevent Tie2 from inhibiting vascular permeability. The classic complement pathway, rather than the alternative complement pathway, is shown. VEGFR denotes vascular endothelial growth factor receptor.

receptor, speculation has centered on the role of the bradykinin B1 receptor. Although the bradykinin B1 receptor is not expressed in normal tissue, inflammatory stimuli, as well as engagement of the bradykinin B2 receptor, can induce its expression.[9,11] Unlike the bradykinin B2 receptor, which is rapidly desensitized, the bradykinin B1 receptor is only slowly and partially desensitized after binding with its agonist. Ex vivo experiments have provided evidence that bradykinin B1 receptor may be expressed during angioedema attacks, which could explain the protracted duration of the swelling episodes.[24]

The mechanism of swelling in hereditary angioedema with normal C1 inhibitor levels is less well characterized but is thought to involve enhanced bradykinin signaling. The disorder is classified into subtypes according to the associated genetic mutation: a mutation affecting factor XII,[25,26] angiopoietin-1,[27] plasminogen,[28] or kininogen-1 heavy chain[29] or an unknown genetic mutation (Table 1). The most common, the factor XII gene mutation, p.Thr309Lys, was found to cause a reduced threshold for activation of the contact system in vitro and in vivo.[34] Factor XII mutations also create new plasmin cleavage sites[35] and, thus, potential pathways for contact-system activation.

The mechanisms underlying angioedema in hereditary angioedema with plasminogen dysfunction,[28] hereditary angioedema with angiopoietin-1 (*ANGPT1*) dysfunction,[27] and hereditary angioedema with kininogen-1 heavy-chain dysfunction[29] are unclear. The plasminogen mutation may relate to the role of plasmin in activation of the contact system. The *ANGPT1* mutation prevents the multimeric protein aggregation that is necessary for Tie2 receptor blockade. Tie2 plays a role in limiting vascular permeability from multiple mediators.[27] The majority of patients who have hereditary angioedema with normal C1 inhibitor levels remain in the unknown-mutation category, for which many potential pathogenic explanations remain to be investigated.

HEREDITARY ANGIOEDEMA WITH C1 INHIBITOR DEFICIENCY

CLINICAL FEATURES

The most important step in making a diagnosis of hereditary angioedema with C1 inhibitor de-

Table 1. Clinical and Laboratory Features of Bradykinin-Mediated Angioedema, According to Type.*

Variable	HAE-C1-INH†	HAE-nl-C1-INH‡	INHA	Acquired C1-INH Deficiency	ACE-Inhibitor–Induced HAE
Clinical features	Recurrent cutaneous and submucosal angioedema without urticaria Attacks prolonged (>48 hr) Physical prodrome of erythema marginatum in approximately one third of patients	Phenotypic presentation similar to HAE-C1-INH Absence of erythema marginatum Rare cutaneous hemorrhage May have more disease-free intervals than with HAE-C1-INH	Similar to HAE-C1-INH	Phenotypic presentation similar to HAE-C1-INH Associated antibodies to C1-INH§ Cancer (e.g., non-Hodgkin's B-cell lymphoma)§	More common in blacks and smokers Less common in patients with diabetes
Genetic features	AD, full penetrance Approximately 75% of patients have positive family history; 25% have de novo mutation (no family history)	AD, incomplete penetrance, female predominance (males can be silent carriers, particularly in subtype HAE-XII)	None	None	None
Attack location	Extremity and abdominal attacks more frequent than facial attacks	Facial attacks most frequent, then extremity attacks, then abdominal attacks More cutaneous and abdominal attacks in subtype HAE-FXII than in HAE-U Characteristic tongue swelling in subtype HAE-PLG	Face and periorbital areas	Facial attacks most frequent, followed by peripheral, abdominal, and oral attacks	Head (tongue) and neck
Age at onset	Childhood or young adulthood, worsening in puberty	Usually after childhood	Usually about 30–40 yr	Usually >40 yr	Usually >40 yr
Triggers	Often unpredictable; stress, trauma, infection, estrogen, fatigue	Often unpredictable; stress, trauma, infection, estrogen, fatigue; greater influence of estrogen in HAE-FXII than in HAE-U	Unknown	May be affected by underlying disorder Often unpredictable; stress, trauma, infection, estrogen, fatigue	ACE-inhibitor use; ARBs are usually associated with an acceptable side-effect profile
C4	Decreased	Normal	Normal	Decreased more than with HAE-C1-INH	Normal
Antigenic C1-INH	Subtype I, decreased; subtype II, normal	Normal	Normal	Decreased or normal	Normal
Functional C1-INH	Decreased	Normal	Normal	Decreased	Normal
C1q	Normal¶	Normal	Normal	Normal or decreased‖	Normal
C3	Normal	Normal	Normal	Normal or decreased	Normal

* Information in the table is modified from Wu et al.[30] ACE denotes angiotensin-converting enzyme, AD autosomal dominant, ARB angiotensin-receptor blocker, C1-INH C1 inhibitor, HAE hereditary angioedema, HAE-C1-INH HAE with low functional C1-INH, HAE-FXII HAE with coagulation factor XII mutation, HAE-KNG1 HAE with kininogen-1 mutation, HAE-nl-C1-INH HAE with normal C1-INH, HAE-PLG HAE with plasminogen mutation, HAE-U HAE with unknown mutation, and INHA idiopathic nonhistaminergic angioedema.
† Subtypes are HAE type I and HAE type II.
‡ Subtypes are HAE-U, HAE-FXII, HAE-PLG, HAE-ANGPT-1, and HAE-KNG1.
§ This feature is seen in some patients and should therefore be included in the evaluation.
¶ On rare occasions, a decrease in homozygous HAE occurs.[31-33]
‖ C1q may be normal in some patients.

ficiency is to maintain a high index of suspicion. Recurrent attacks of cutaneous angioedema (asymmetric, nonpruritic, disfiguring, and nonpitting) without urticaria or spontaneously remitting, severe abdominal symptoms (pain and swelling) or both should alert the clinician to consider hereditary angioedema. Although cutaneous and abdominal attacks are the most common feature, patients infrequently have genital swelling and, in rare cases, bladder, muscle, or joint swelling. Laryngeal episodes account for approximately 0.9% of all attacks; however, all patients are at risk for a laryngeal attack, and more than 50% have a laryngeal attack during their lifetime.[8,36] A lethal laryngeal attack can be the initial presentation.[37]

Hereditary angioedema with C1 inhibitor deficiency typically develops in childhood (mean age at onset, 8 to 12 years), rarely occurs before 1 year of age, and usually worsens during puberty. The disease can fluctuate during a patient's lifetime and, as in the vignette, may vary in severity among members of the same genetic kindred. An early onset may be associated with more severe disease.[38]

Hereditary angioedema with C1 inhibitor deficiency is an autosomal dominant disorder (prevalence, approximately 1 case per 50,000 persons). Because it is rare, the condition is often not recognized.[39] Consequently, patients may receive treatments that target histamine-mediated or mast-cell–mediated angioedema (i.e., glucocorticoids, antihistamines, and epinephrine), which are ineffective for hereditary angioedema.[40] Some patients are accused of drug-seeking behavior because of multiple urgent visits for pain relief. Submucosal angioedema of the intestine can mimic an acute abdomen, resulting in unnecessary surgery. Peripheral attacks are associated with clinically significant morbidity.[41] Although the interval between the onset of symptoms and diagnosis has decreased from earlier reports of approximately 22 years, delays remain unacceptably long at 8 to 10 years.[38-40] A family history, as in the case of the patient in the vignette, does not always translate into an earlier diagnosis.[39]

Patients frequently report a variety of prodromal symptoms before the onset of an attack, including a distinctive, nonpruritic, serpiginous rash, erythema marginatum, in approximately one third of patients. Although erythema marginatum is the most specific prodrome in hereditary angioedema, its presence has been associated with diagnostic delay, presumably because of confusion with urticaria.[42] Tingling, fatigue, asthenia, and discomfort at the site of emerging swelling have also been reported as prodromal symptoms.

Explanations for the initiation of an attack have remained elusive. Among reported triggering factors, stress is the most frequently cited.[43] Surgery, medical procedures (e.g., colonoscopy), trauma, infections, and fatigue are also recognized as precipitants. Angiotensin-converting–enzyme inhibitors, which block bradykinin catabolism, are contraindicated because of the risk that they will exacerbate hereditary angioedema. Exogenous estrogens should be avoided because of their well-recognized potential for increasing the severity of the disease. The effect of gestation on hereditary angioedema varies among women, as well as among those who have subsequent pregnancies. Delivery is usually uncomplicated.

LABORATORY DIAGNOSIS

Type I hereditary angioedema with C1 inhibitor deficiency accounts for 85% of cases, and type II accounts for 15% (Table 1). Both types are characterized by low serum C4 levels from activation of the complement cascade, for which C1 inhibitor is a key regulatory protein. The case described in the vignette is classified as hereditary angioedema type I, with low antigen and functional C1 inhibitor levels. Patients with hereditary angioedema type II have normal antigen levels but low C1 inhibitor function as a result of mutations affecting the reactive loop of the molecule. Hereditary angioedema types I and II are phenotypically indistinguishable.[8] C1q levels are characteristically normal but were low in three of the four rare homozygous cases of the disease that have been described.[31-33]

The increased risk of asphyxiation and death for patients without an established diagnosis provides a compelling impetus to urge all family members of an index patient to be tested.[36] Two types of C1 inhibitor functional analyses are available. The chromogenic assay (recommended when available) is more sensitive than the enzyme-linked immunosorbent assay.[44] For children, measurement of the C4 level and the C1 inhibitor level appears to be accurate during the first year of life but should be repeated for

verification.[45] Genetic sequencing (if the mutation is known) can be used to establish an early diagnosis.[45,46]

The distinction between angioedema mediated by bradykinin and angioedema mediated by mast cells or histamine is critical, with implications for morbidity, mortality, and treatment (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

GENETIC TESTING

More than 400 deficiency-causing mutations in *SERPING1* have been identified. Only 1 has been associated with a normal phenotype in which the mutant protein failed to complex with C1r but retained the ability to inhibit kinin-generating enzymes.[47] Approximately 25% of mutations are de novo. Hereditary angioedema with C1 inhibitor deficiency has full penetrance and does not vary according to race or ethnic group.[8] In a small minority of patients (5 to 10%), no pathogenetic variant is detected in *SERPING1*.[18,20,48,49]

Gene sequencing is usually not required for the diagnosis but has been instrumental in establishing a diagnosis in rare cases. Hereditary angioedema type I has been detected in two sisters with unaffected parents, as a result of paternal gonadal mosaicism.[50] A recessive pattern of inheritance has been reported[51] for an Arg378Cys *SERPING1* mutation, which appears to be unusually sensitive to intracellular stress, affecting protein folding and secretion. The mutation results in intermittent disease expression and fluctuation in C1 inhibitor and C4 levels. Severe disease has been described in a patient with an Arg378Cys homozygous mutation[32] whose heterozygous relatives did not have a hereditary angioedema phenotype. Other reported cases of homozygous hereditary angioedema with C1 inhibitor deficiency have varied in severity, underscoring the importance of disease-modifying influences beyond C1 inhibitor mutations that have yet to be clearly elucidated.[31,33]

HEREDITARY ANGIOEDEMA WITH NORMAL C1 INHIBITOR LEVELS

CLINICAL FEATURES

A third group of patients with hereditary angioedema, those with normal levels of C1 inhibitor, was first reported in 2000.[6,7] The clinical presentation is phenotypically similar to that of hereditary angioedema with C1 inhibitor deficiency, with prolonged attacks of cutaneous and submucosal swelling (lasting for approximately 2 to 5 days). Hereditary angioedema with normal C1 inhibitor levels has an autosomal dominant inheritance pattern with incomplete penetrance. Men can be silent carriers of the disease. Hormonal influences of pregnancy or exogenous estrogens may be pronounced, particularly in patients who have hereditary angioedema with a factor XII mutation.[6,25] Sites of swelling and attack frequency differ slightly between hereditary angioedema with C1 inhibitor deficiency and subgroups of hereditary angioedema with normal C1 inhibitor levels (Table 1).[6,25,52]

DIAGNOSIS

Establishing a diagnosis of hereditary angioedema with normal C1 inhibitor levels is hampered by an absence of commercially available biomarkers, with the exception of the known genetic mutations (which appear to be rare or have yet to be reported in the United States).[26-29] A promising assay to identify persons with kinin-mediated angioedema has recently been described.[53] At present, the diagnosis of hereditary angioedema with normal C1 inhibitor levels is based on consensus guidelines.[54] These criteria, along with supportive data, known mutations, and emerging biomarkers, are outlined in Table 2.

ADVANCES IN THE TREATMENT OF HEREDITARY ANGIOEDEMA

The case vignette illustrates the dramatic improvements in the management of hereditary angioedema. In the past, antifibrinolytic agents (tranexamic acid or epsilon aminocaproic acid) and attenuated androgens such as danazol were the primary options for short- and long-term prophylactic care. The mechanism of action of danazol remains largely unknown but is postulated to include induction of metallopeptidases, which inactivate bradykinin, and increased production of functional C1 inhibitor.[55] Although these treatments are effective, outcomes have fallen far short of the goal of normalizing patients' lives, and there is a risk of serious side effects, as highlighted in our case vignette. At present, these agents are considered second-line therapies.

Until 2009, there were no FDA-approved therapies for attacks of angioedema, with options limited to supportive care and efforts to protect the airway. Fresh-frozen plasma was an exception, which although helpful in some cases, carried the risk of escalating the severity of an attack.[8] In the past decade, several on-demand treatments have been approved. Each agent targets disruption of the contact-system cascade's mediation of vascular leakage through bradykinin generation. Although the availability of these therapies for acute attacks has eased the burden of disease, persistent psychological effects, disruption of daily life, fear of suffocation, and fear of having a child with hereditary angioedema continue to have a substantial effect on the lives of patients.[56]

Intravenous plasma-derived C1 inhibitor (Cinryze) was the first new targeted prophylactic therapy approved by the FDA for the treatment of hereditary angioedema with C1 inhibitor deficiency.[57] The burden of receiving intravenous treatment at infusion centers was partially ameliorated by self-administration.[58] Problematic venous access (involving clotting and infection) led to the placement of indwelling ports for many patients. As in the case vignette, additional treatment did not always result in complete disease control. A major advance in prophylactic care for hereditary angioedema has been the approval of subcutaneous treatments, including plasma-derived C1 inhibitor[22] and lanadelumab, a human monoclonal inhibitor of plasma kallikrein, in both cases circumventing the requirement for intravenous access and showing improved efficacy. As illuminated in the case vignette, the superior control achieved with these treatments approaches the goal of normalizing patients' lives.

The principles guiding the management of hereditary angioedema are outlined in Table S2. Currently approved front-line therapies are discussed below and listed in Table 3. Their sites of action are shown in Figure 1.

Table 2. Diagnosis of Hereditary Angioedema with Normal C1 Inhibitor Levels.

Consensus criteria*

History of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema
Normal or near-normal C4 level and C1 inhibitor antigen level and function
Documented lack of response to high-dose antihistamines (e.g., second-generation antihistamines given 4 times/day)
Either a known genetic mutation (factor XII, angiopoietin-1, plasminogen, or kininogen-1) or a family history of angioedema†

Supportive data

History of no response to epinephrine and glucocorticoids
History of prompt and durable responses to a bradykinin-targeted medication‡
Documented, visible angioedema or, in patients with predominantly abdominal symptoms, evidence of bowel-wall edema identified by computed axial tomography or magnetic resonance imaging§

Emerging biomarkers

Threshold-stimulated kallikrein activity¶

* All four criteria must be met. If there is no family history and no biomarker has been determined, compelling supportive data may suggest the diagnosis.
† Mutational analysis for plasminogen, angiopoietin-1, and kininogen-1 is available only at a limited number of research facilities.
‡ Prompt, durable responses are those that occur within 30 to 120 minutes after administration of the medication and that last for more than 6 hours.
§ Ultrasonography could be used, although it is less sensitive. In the case of negative findings, we recommend computed axial tomography or magnetic resonance imaging.
¶ The assay for this biomarker has been described by Li et al.[44]

ON-DEMAND TREATMENT FOR ACUTE ATTACKS

Our improved understanding of the pathophysiological mechanism of swelling has catalyzed the design and approval of four specific products for on-demand use in the management of hereditary angioedema. These treatments for acute attacks replace plasma-derived C1 inhibitor (Berinert, CSL Behring) and recombinant human C1 inhibitor (Ruconest, Pharming), inhibit the bradykinin B2 receptor (icatibant), or inactivate plasma kallikrein (ecallantide). Each has been shown in randomized, controlled studies to be effective and safe for the management of hereditary angioedema with C1 inhibitor deficiency.[59-61] Subsequent data from open-label extension studies, along with registry data, have underscored the continued efficacy and safety of these drugs.[62-66]

No randomized, controlled studies of on-demand treatment in patients with hereditary angioedema and normal C1 inhibitor levels have been completed. However, numerous open-label studies have revealed successful responses to each of the on-demand treatments used for hereditary angioedema with C1 inhibitor deficiency.[26]

SHORT-TERM PROPHYLAXIS

Short-term prophylaxis for hereditary angioedema with C1 inhibitor deficiency may be indicated before medical, surgical, or dental procedures, which are known triggers of swelling.[37,40] The preferred prophylaxis is C1 inhibitor, adminis-

tered 1 to 12 hours (ideally within 2 hours) before the procedure. In the event that plasma-derived C1 inhibitor is unavailable, fresh-frozen plasma (2 units administered 1 to 12 hours before the procedure) or an attenuated androgen (danazol at a dose of 400 to 600 mg per day, started 5 to 7 days beforehand) can be used. Icatibant, ecallantide, and recombinant human C1 inhibitor are not recommended as short-term prophylaxis because of their shorter half-lives.

Scant data are available regarding short-term prophylaxis for hereditary angioedema with normal C1 inhibitor levels. The same approach may be tried, with the important caveat that on-demand therapy should be available in case it is needed.

LONG-TERM PROPHYLAXIS

Intravenous C1 Inhibitor Replacement

Plasma-derived C1 inhibitor (Cinryze) was approved by the FDA in 2008 as long-term prophylaxis in adolescents and adults who have hereditary angioedema with C1 inhibitor deficiency, on the basis of evidence that such treatment reduces attacks by approximately 50%.[57] With favorable outcomes of a phase 3 study, the indications were expanded in 2018 to include treatment of children as young as 6 years of age.[67] Open-label extension data for these patients revealed improved outcomes with continued use and safety with long-term exposure. Reduction of the standard 3-to-4-day dosing interval has been used, as in our case vignette, as has dose escalation.[68,69] Favorable phase 2 data have also been published for long-term prophylaxis with recombinant human C1 inhibitor in patients who have hereditary angioedema with C1 inhibitor deficiency.[70] Prophylactic treatment with plasma-derived C1 inhibitor has also been effectively used for patients who have hereditary angioedema with normal C1 inhibitor levels, with or without factor XII mutation,[26] including pregnant women.[71] However, controlled studies are needed to support the general use of C1 inhibitor in this patient population.

Subcutaneous C1 Inhibitor Replacement

Subcutaneous C1 inhibitor is highly effective in preventing angioedema attacks in patients who have hereditary angioedema with C1 inhibitor deficiency. The pivotal phase 3a placebo-controlled, crossover trial showed a 95% reduction in the median attack rate with subcutaneous C1 inhibitor administered at a dose of 60 IU per kilogram of body weight, with a corresponding dramatic reduction in rescue medication, leading to FDA approval.[22] The ability to achieve steady-state C1 inhibitor activity of more than 40% appears to be key to the efficacy of this treatment. A post hoc analysis showed a meaningful improvement in measures of health-related quality of life.[72]

Monoclonal Antibody Inhibitor of Plasma Kallikrein

Lanadelumab, a subcutaneously delivered, fully human monoclonal antibody inhibitor of plasma kallikrein, was analyzed in a phase 3 placebo-controlled, parallel-group study. Over a 26-week period, treatment with 300 mg of lanadelumab every 4 weeks or 300 mg every 2 weeks significantly decreased attack rates by 73.3% and 86.9%, respectively, in patients who had hereditary angioedema with C1 inhibitor deficiency. Use of on-demand treatment and rates of high-morbidity attacks were substantially reduced.[73] As with subcutaneous C1 inhibitor therapy, measures of quality of life improved during the study.[73] Lanadelumab is approved at a dose of 300 mg every 2 weeks, with guidance to consider administering 300 mg every 4 weeks in patients with stable (i.e., attack-free) disease after 6 months.

Since hereditary angioedema with normal C1 inhibitor levels appears to involve bradykinin generation by plasma kallikrein, lanadelumab may be an effective therapy in patients with this type of disease. However, data are not available to support treatment in such patients.

Hormonal Therapy

Given the prominent role of estrogens in escalating disease severity in patients who have hereditary angioedema with normal C1 inhibitor levels, withholding exogenous estrogens is a first step in the treatment of this subgroup of patients. Progestins have been shown to be beneficial for prophylactic treatment of hereditary angioedema with normal C1 inhibitor levels.[26] In the United States, norethindrone (0.35 mg per day) has been used, although dosing standards have not been established. In addition, the benefits of treatment with attenuated androgens have been documented in multiple cases of hereditary angioedema with normal C1 inhibitor levels, with the same concerns regarding an adverse side-effect profile.[26]

Table 3. First-Line Treatments for Hereditary Angioedema with C1 Inhibitor Deficiency.*

Drug (Trade Name, Manufacturer)	Approved Indications†	Dose	Mechanism of Action	Potential Side Effects
Plasma-derived C1 inhibitor (Berinert, CSL Behring)	Acute attacks in all age groups, including women who are pregnant or breast-feeding	20 U/kg IV	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Recombinant human C1 inhibitor (Ruconest, Pharming)	Acute attacks in adolescents and adults, including women who are pregnant or breast-feeding	50 U/kg IV (maximum dose, 4200 U)	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis (among rabbit-sensitized persons) Theoretical: transmission of infectious agent
Ecallantide (Kalbitor, Takeda)	Acute attacks in patients ≥12 yr of age	30 mg SC	Inhibits plasma kallikrein	Common: prolonged PTT‡ Rare: risk of anaphylaxis§ Uncommon: antidrug antibodies
Icatibant (Firazyr, Takeda)	Acute attacks in patients ≥18 yr of age¶	Adults: 30 mg SC Children: 12–25 kg, 10 mg SC 26–40 kg, 15 mg SC 41–50 kg, 20 mg SC 51–65 kg, 25 mg SC >65 kg, 30 mg SC	Bradykinin B2 receptor antagonist	Common: discomfort at injection site
Plasma-derived C1 inhibitor (Cinryze, Takeda)	Prophylaxis in patients ≥6 yr of age‖	Children (6–11 yr): 500 U IV every 3–4 days; doses up to 1000 U IV every 3–4 days may be needed Adolescents >12 yr of age and adults: 1000 U IV every 3–4 days; doses up to 2500 U IV every 3–4 days may need to be considered on the basis of a patient's response	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Plasma-derived C1 inhibitor (HAEGARDA, CSL Behring)	Prophylaxis in patients ≥12 yr of age	60 U/kg SC twice weekly	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Common: mild injection-site reaction Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Lanadelumab (Takhzyro, Takeda)	Prophylaxis in patients ≥12 yr of age	300 mg SC every 2 wk; 300 mg every 4 wk may be considered if patient is attack-free for >6 mo	Inhibits plasma kallikrein	Common: mild injection-site reaction, dizziness, prolonged PTT‡ Rare: risk of anaphylaxis

* IV denotes intravenously, PTT partial-thromboplastin time, and SC subcutaneously.
† The listed indications are those approved by the Food and Drug Administration.
‡ A prolonged PTT is not clinically significant. The increase is due to inhibition of "feedback" for activation of factor XII by kallikrein.
§ This agent must be administered by a medical professional who is prepared to treat anaphylaxis.
¶ In Europe, this agent is approved for use in patients 2 years of age or older.
‖ This agent is approved in Europe for short-term, on-demand treatment in patients 2 years of age or older.

Antifibrinolytic Agents

Tranexamic acid has been used successfully for prophylaxis in patients who have hereditary angioedema with normal C1 inhibitor levels, with speculation that it reduces the sensitivity to plasmin cleavage.[25,26] Tranexamic acid (Lysteda, Ferring Pharmaceuticals) is available in the United States (usual starting dose, 650 to 1000 mg administered twice a day).[25,26] Adverse events include a slight risk of thrombosis, with additional side effects of gastrointestinal upset, myalgia, and dysmenorrhea.

EMERGING THERAPIES

The goal of treatment for hereditary angioedema is to improve the quality of life for patients, not only by decreasing the frequency and severity of attacks but also by providing therapies that are easy to administer and have minimal side effects. Table S3 details the emerging therapies for hereditary angioedema and genetic modification, with their stages of development.

CONCLUSIONS

In the past, patients with hereditary angioedema often had anxiety, depression, and disruption of work, school, and daily life. An improved understanding of the pathophysiology of hereditary angioedema and classification of phenotypes has driven the investigation of new and targeted therapies. On-demand treatments have incrementally enhanced patients' safety and quality of life. Effective and safe prophylactic treatments now provide a pathway toward a normal life. A shift in the treatment paradigm toward the expanded use of prophylaxis is anticipated, which should ameliorate the ever-present fear of disfiguring, painful, or fatal attacks. With appropriate care, the next generation of patients with hereditary angioedema may no longer have to experience the burden of what has been labeled a catastrophic disease.[74]

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