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Long-term outcome of C1-esterase inhibitor deficiency

Luong Hoang Long,[1] Tatsuya Fujioka,[1] Timothy J Craig,[2] Hirofumi Hitomi[1]

Abstract

Hereditary angioedema (HAE) is a rare hereditary disorder characterized by episodic swelling and life-threatening airway obstruction caused by laryngeal angioedema. In most HAE patients, reduced level of serum C1-Inhibitor (type-I-HAE) or presence of aberrant C1-Inhibitor (type-II-HAE) result in the lost of regulation of the complementary system and contact activation system with downstream over-activation of bradykinin – the chief mediator leading to angioedema. Type-III HAE (HAE-nl-C1INH) is rare without deficient or dysfunction of C1-Inhibitor, often with genetic aberrant related to the contact activation system. The prevalence of HAE in the population is estimated at 1 in 50,000 individuals, often with early onset, but due to the heterogeneity of the disease, there is frequently a significant delay in diagnosis. Recently, better awareness by physicians, more access to diagnostic tools, better management and prophylaxis has decreased morbidity and mortality. A focus in HAE patient care shift from management of attacks with on-demand medication, to use of prophylaxis to reduce attacks has improved the overall quality of life of patients with HAE. One area in HAE research that has not been emphasized is the long-term consequence of C1-INH deficiency in HAE patients, other than the typical manifestations of HAE, as evidence have emerged linking this disorder with increased risk of cardiovascular diseases, auto-immune disorders, and malignancy. This review aims to gather the current knowledge and evidence of potential consequence of C1-Inhibitor deficiency in HAE aside from angioedema with emphasis in the improvement of long-term care and overall quality of life for HAE patients.

Key words: Hereditary angioedema, C1-Inhibitor, complementary, contact-activation system, complement system, contact pathway, C1-esterase inhibitor, C1-esterase inhibitor deficiency

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Affiliations:
[1] Department of iPS Cell and Regenerative Medicine, Kansai Medical University, Japan.
[2] Departments of Medicine, Pediatrics, Biomedical Sciences, Penn State University, Hershey, PA, USA

Corresponding author:
Hirofumi Hitomi
2 Chome-5-1 Shinmachi, Hirakata, Osaka 573-1191
E-mail: hitomih@hirakata.kmu.ac.jp

Abbreviations:

AD	Autoimmune disease
BBB	Blood-brain barrier
C1-INH	C1 Inhibitor
FLA	Fatal laryngeal attack
HAE	Hereditary Angioedema
HAE-nl-C1-INH	Hereditary Angioedema with normal level of C1-INH
HAEA	Hereditary Angioedema Association Advisory board

Abbreviations (Continued):

HK	High molecular weight kininogen
LTP	Long-term prophylaxis
MASP	Manose-binding Lectin-associated Serine protease
SERPIN	Serine Protease Inhibitor

Hereditary angioedema – The complementary system and contact activation system

Hereditary angioedema etiology and classification

The core etiology of Hereditary angioedema (HAE) is the dysregulation of an innate inflammatory pathway, where the over-activation of bradykinin binds on to the bradykinin receptor and leads to the weakening of the endothelial intercellular junction and subsequent extravasation of vascular fluids into the surrounding tissue.[1–3] Most patients with HAE carry a heterozygous defect in the *SERPING1* gene which encodes for C1-INH (C1-Esterase Inhibitor or C1-Inhibitor) protein. In most case this can lead to a quantitative decrease in serum C1-INH level (HAE type I – 85% of cases) or less commonly normal serum level of C1-INH, but with impaired functionality (HAE type II ~15% of cases).[1] HAE with normal C1-inhibitor, or HAE-nl-C1-INH, is a rare subtype of HAE often with defect of component downstream of C1-INH (FXII, plasminogen, kininogen, angiopoetins…)

or unknown genetic aberration.[2,4,5] In this article, HAE will mostly refer to patients with type I and type II HAE unless otherwise specified as HAE-nl-C1-INH. C1-INH is produced mainly in hepatocytes along with most complement components, thus HAE has been argued by some authors to be a liver metabolic disorder, similar to other hereditary diseases such as Alpha-I antitrypsin deficiency (AATD) or Wilson's Disease.[6]

In most case of HAE type I and II, even with one functional copy of SERPING1 gene, the actual functional C1-INH serum level frequently falls below 35% instead of the theoretical 50%.[7] This is observed in some case to be due to the "trans" inhibition of the wild-type *SERPING1* copy by the pathogenic copy.[8] Other explanation involve the build-up of misfolded product in the endoplasmic reticulum (ER) leading to ER stress and reduction of the overall protein production (**Figure 1A**).[9,10] The full extend and exact mechanism of this phenomenon is still under investigation, however it might explain the heterogeneity in frequency and severity of attacks among HAE patients.

The classical complement pathway

Complementary is a fast-acting, first line immunosurveillance system that is both ancient and evolutionary conserved,[11] evidence of complementary system can be found in organism as simple as sponges (porifera).[12] The complementary system in human and higher vertebrate consist of around 60 membrane-bound and secreted protein components.[11,13] The complement system maintains a low but constant auto-activation (tick-over) on healthy human cells to ensure timely response to any invading pathogens or abnormal cells, this tick-over probing and potential activation of complement cascade is controlled by a number of soluble and cell-bound regulators.[11,13,14] Inadequate level of complement regulators to control and orchestrate complement response can tip the balance toward inflammatory, and subsequent cascading events can wreck havoc on the host.

C1-INH, as the numbering suggest, is the soluble inhibitor of the first component in the complement pathway, which is also called the complementary system, specifically it inhibits C1r/s and the subsequent formation of the complete C1 complex (C1q.r2.s2). C1-INH also binds and regulates components of different pathways (fibrinolytic, coagulation, and kinin-forming systems). C1-INH belongs to a class of molecules called SERPIN (Serine Protease Inhibitor) that consist of a bait sequence that mimics the target enzyme's substrate. Upon being cleaved, C1-INH form a strong covalent bond with its target (C1q, C1r and MASP [Manose-binding lectin-associated serine protease]), exhausting itself in the process. Hence an adequate level of C1-INH needs to be maintained at all times to ensure proper control of complement activation. In HAE patients, an abnormally low level of C1-INH or impaired C1-INH function, coupled with attack signals overload (stress, infection, surgical procedure, trauma) will further deplete the remaining C1-INH below a critical threshold (identified at approximately 38-40%).[15,16] Without any checks, the first component of the classical pathway, C1r autoactivates via intramolecular autocatalysis,[14] cleaving C1s, which in turn activates C2 then C4. C4 is depleted in the process, and at times C2 during attacks, however, the next component of the complement system, C3, remains at a stable level even during attacks, but is moderately activated (**Figure 1B**).[17–19] The classical pathway doesn't directly contribute to the clinical symptom of HAE, however the long-term effect of over activation of the complement system has yet to be studied in depth.

The contact activation and plasma kallikrein/kinin system

C1-INH, aside from its role in the classical complementary system, is also responsible for the inhibition of contact activation factors, it is the main inhibitor (93%) of activated FXII in plasma[20] and partially responsible for the inhibition of prekallikrein (52%).[21] Contact activation system, specifically the nonapeptide Bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-OH) have been identified to be the main pathway/factor leading to extravasation and clinical swelling in HAE patients.[22] In plasma, a fraction of XII autoactivates secondary to contact with negatively charged surface or other analogues,[23] resulting in activated XII (XIIa) that activates prekallikrein to plasma kallikrein, which in turn forms a positive feedback loop with XIIa to exponentially ramp up XIIa activation. This loop is further amplified by high molecular weight kininogen (HK). During this process, plasma kallikrein cleaves HK to release bradykinin (the plasma kallikrein/kinin system),[24] a very potent vasodilator. Through interaction with Bradykinin B2 receptor (B2R, *Bdkrb2*) on vascular endothelial cells, bradykinin affects the cell junction's permeability,[25] facilitates production of cGMP, NO and prostacyclin, which results in vascular leakage and fluid extravasation[26] (**Figure 1B**). The chronic disruption to the kallikrein/kinin system, aside from causing inflammation and swelling, have been implicated in multiple other disease processes.

Diagnosis And Management Of Hereditary Angioedema

Diagnosis of Hereditary Angioedema

HAE is considered a rare disease with the prevalence of HAE in the US population is estimated at 1 in 50,000 individual,[27,28] but due to the heterogeneity of the disease there is often a significant delay in diagnosis of this disorder. One survey conducted by the US HAE Association suggest an average 8.6 years lag between onset of first symptom and diagnosis.[29] The 2020 guideline for the management of hereditary angioedema by the US HAEA (Hereditary Angioedema Association Advisory board)[30] had laid out in detail the recommendations for diagnosis, classification, treatment, prophylactic medications, long-term management and other specific considerations.

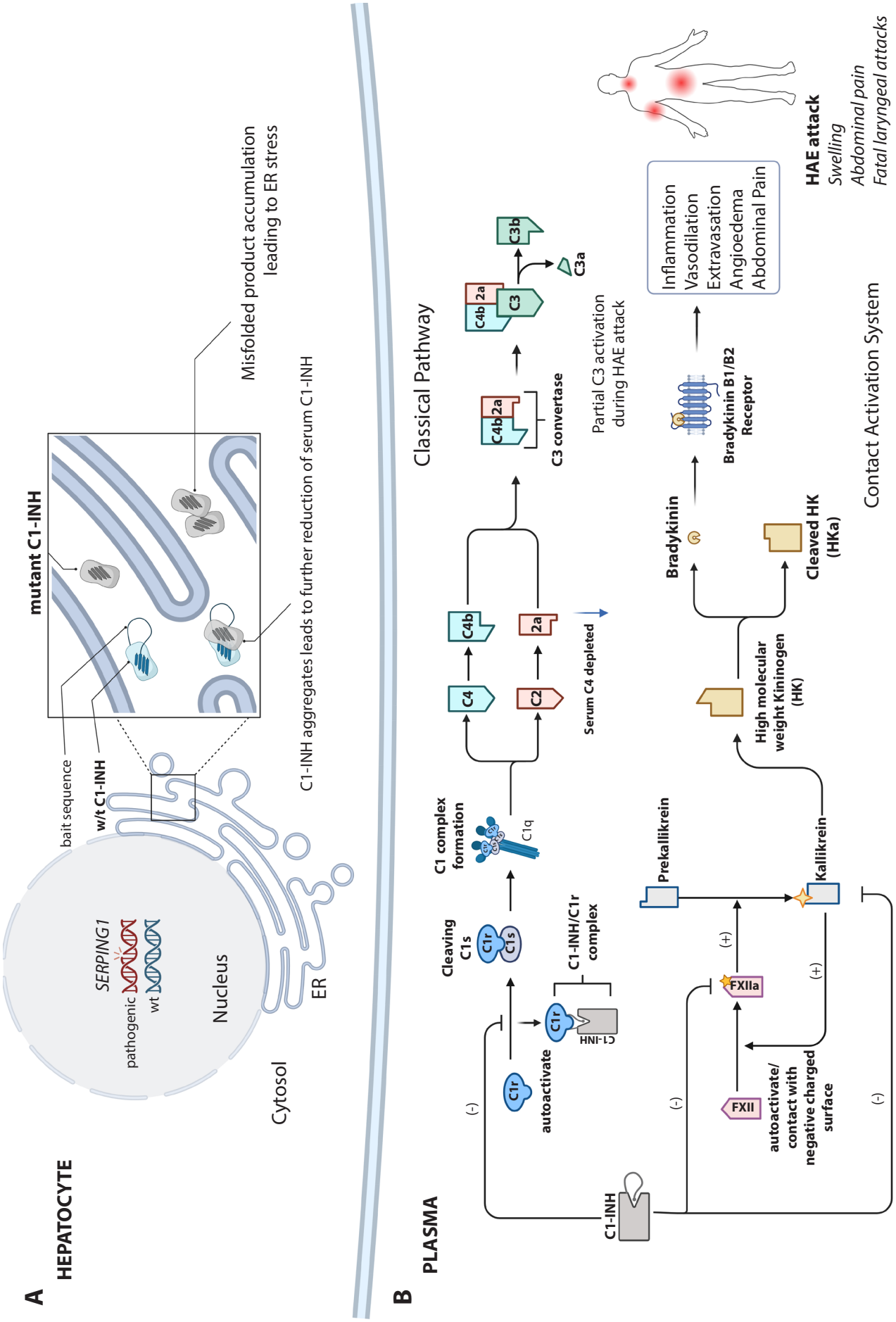

Figure 1. Hereditary angioedema disease etiology and related pathways. (A) Most HAE patients (type I/II) carry one pathogenic copy of *SERPING1*. Serum C1-INH however often fall below 38% instead of the theoretical 50%, this is suggested to be due to ER stress by misfolded products or in some case aggregation between the wild-type and misfolded C1-INH in ER. (B) Reduction and depletion of serum C1-INH leads to over-activation of both the complement classical pathway and the contact activation system, with the later directly leads to clinical symptoms of HAE attack.

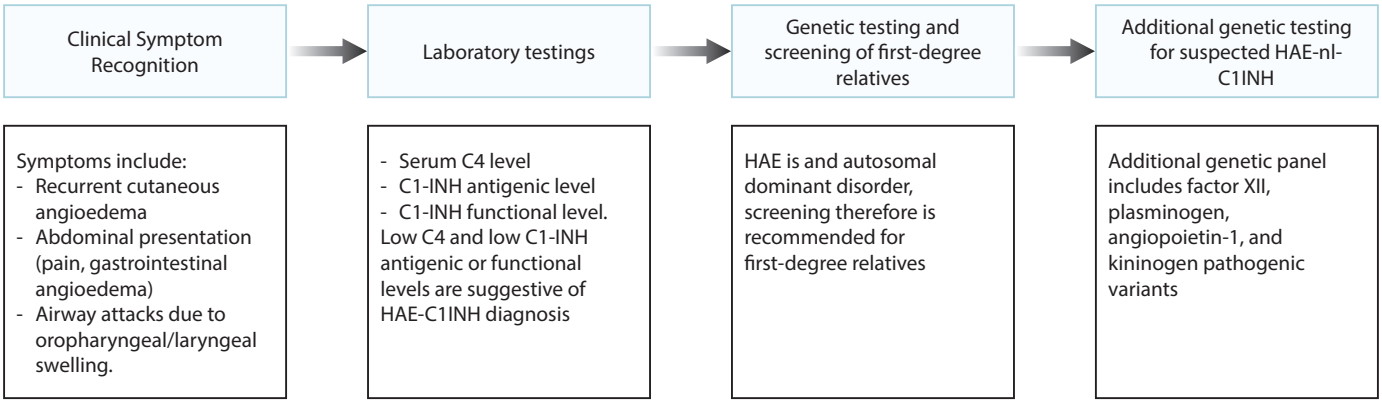

Figure 2. Recommended diagnostic workflow of Hereditary Angioedema based on the US HAEA 2020 guideline.

The diagnosis of Hereditary Angioedema (HAE) involves clinical evaluation, biochemical testing, and at times genetic testing, to confirm the presence of mutations associated with the disorder, as well as additional screening for first degree-relatives and extra genetics panel when C1-nl-INH is suspected. **Figure 2** shown the recommended diagnostic workflow based on the US HAEA 2020 guideline.[30]

Management of Hereditary Angioedema

Management should include on-demand treatment for acute attacks with C1 inhibitor replacement therapy, kallikrein antagonist or bradykinin receptor antagonists, and long-term prophylaxis using C1 inhibitor replacement therapy, kallikrein antagonists, or other options based on individual patient factors.[31–33] Short-term prophylaxis is recommended when the patients are subjected to known triggers that may illicit a HAE attack such as dental, surgical or other invasive medical procedures.[30]

Regular follow-up and communication between patients and healthcare providers are crucial for optimizing treatment plans and addressing any changes in the course of HAE. These guidelines together with other resources, recent awareness, physician education and nation-based patient support groups for HAE have significantly improved the time to diagnosis of HAE patients. Early diagnoses and proper management of HAE patients should lower the risk of fatal laryngeal attacks (FLA),[34] reduce disability, anxiety, and post-traumatic stress syndrome, and hopefully result in health and lifespan comparable with the general population.[35] Focusing on high risk and unique cohorts of the HAE population, such as children, women, pregnancy, lactation, elderly and menopause is important to ensure improved quality of life, normalcy and longevity of HAE patients.[36,37] Although further research is necessary, recent clinical and experimental studies suggested that the dysregulation of the many pathways involved in HAE may lead to an increase of other pathologies other than the recurrent angioedema.

Hereditary angioedema and chronic comorbidity

Diagnosis of Hereditary Angioedema

Most of recent guidelines have not specifically addressed the connection between C1-INH deficiency in Hereditary Angioedema (HAE) patients, and the dysregulation of the complement system, contact activation system, coagulation pathway, and the potential risk of chronic diseases.[38–41] Hereditary Angioedema is an uncommon condition with heterogeneous clinical presentation, therefor it can be challenging to gather a large enough cohort to establish clinical connection with any single chronic disease compared with other non-hereditary disorders. The scope of this review therefore is to collect and summarize all available clinical and also experimental evidences linking C1-INH deficiency with long-term disruption of multiple organ systems. Interestingly, several large population-wide comprehensive cohort studies published recently supported the notion that HAE patients have higher risk of suffering from chronic comorbidities compared with matched population controls:

- Sundler et al. (2022)[42] study on 239 Swedish HAE (type I & II) patients with 2383 matched control shown statistically significant increase in risk of autoimmune diseases and cardiovascular disorders, notably hypertension, hyperlipidemia and thrombosis.
- Christiansen et al. (2023)[43] with the data from the US Hereditary Angioedema Association which surveyed 485 HAE-C1INH, 26 HAE-nl-C1INH patients revealed a significantly higher risk of autoimmune disorders, kidney diseases, anemia, hepatitis, angina, depression and sleep disturbance.
- Zanichelli et al. (2024)[44] recently published a cohort of 446 HAE patients, followed up to a 43-year period. A greater prevalence among HAE patients compared with matched population control was found for: heart diseases (9.6% vs. 4.8%), acute myocardial infarction (5.6% vs. 1.4%), HCV infection (10.5% vs. 2.5%), and appendectomy (15.9% vs. 4.3%).

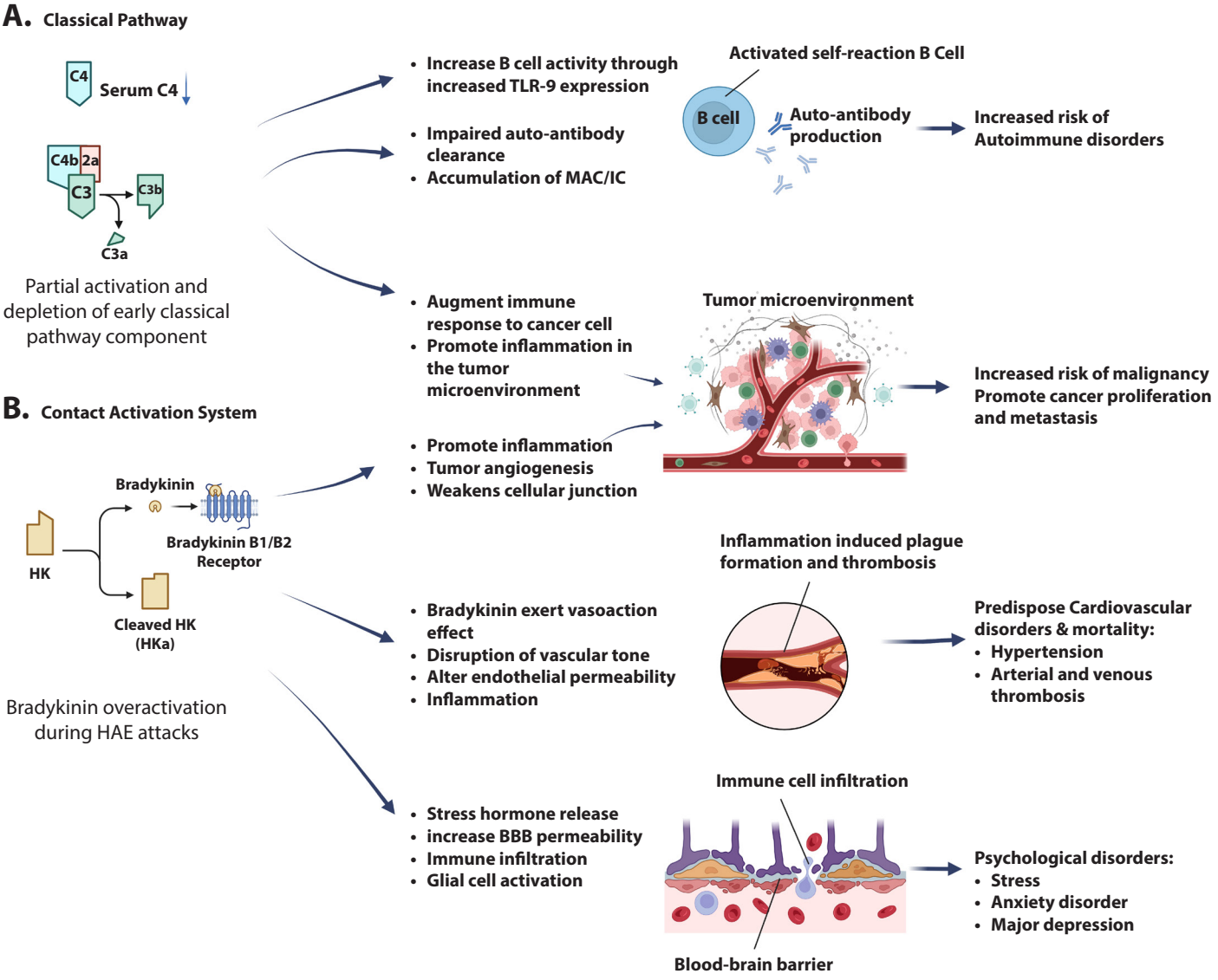

Figure 3. Summary of the perturbed pathways in hereditary angioedema and their respective long-term effects on chronic disease development and progression.

Considering the significance of these complex pathways and their importance in homeostasis and immune surveillance, in conjunction with accumulated clinical and experimental evidence; it is reasonable to speculate that HAE-C1-INH patients face a higher risk of chronic comorbidities, especially for undiagnosed/unmanaged patients. We summarized the affected pathways in HAE and their long-term consequent on chronic disease development and progression in **Figure 3**; **Table 1** compiled and detailed the up to date clinical studies and cohorts of HAE patients comorbidity. **Table 2** outlines the percentage of HAE patients with specific comorbidities, alongside the corresponding data for normal matched controls, OR and 95% CI (confident interval) are included if available. We detailed bellow the currently available evidence for major groups of chronic comorbidity.

HAE and Autoimmune disorder

As discussed earlier, the reduction in C1-INH either quantitatively or qualitatively results in the activation of classical complement system pathways and complement depletion. Evidence of the causative role of C1-INH deficiency with autoimmunity remains under debate. Early component of the classical pathway (C1q, C1r, C1s, C4 and C2) have been found to play a role in immune respond against self-antigen and clearance of immune complexes (ICs), and deficiencies of these complement components have been linked to multiple immunoregulatory disorders.[45] C1q deficiency especially have been associated with development of systemic lupus erythematous (SLE) with more severe manifestations.[46]

Table 1. Summary table of clinical evidences on comorbidities of HAE patients.

Authors/year/reference	Population/sample size	Key findings
Kessel et al., 2012[48]	61 HAE patients (56 type I HAE & 5 type II HAE)	7 patients (11.4%) were diagnosed with an immunoregulatory disorder, patients had high serum autoantibodies (47.5%), and significant increase in B cell activity with expression of TLR-9.
Brickman et al.,1986[50]	157 HAE patients	19/157 (12%) patients were found to have either systemic or organ-specific autoimmune disease
Farkas et al (2011)[52]	130 HAE patients	The incidence of immunoregulatory disorders was 11.5%, compared with 5.2% in non-C1-INH-deficient controls.
Farkas et al (2020)[53]	589 HAE (C1-INH deficiency) patients	76 patients (12.9%) with coexisting autoimmune disease (AD); patients with C1-INH replacement therapy had a lower number of visits for coexisting ADs
Stepaniuk, Kanani, 2021[54]	49 HAE patients (type I &II)	Similar incident of autoimmune disorder (6/49 patients, 12.24%) and malignancy (6/49 patients, 12.24%)
Sundler et al., 2022[97] Grover et al., 2022[70]	Case-control study 239 Swedish HAE (type I & II) patients with 2383 matched control	Significant increase in risk of autoimmune diseases (OR 1.65; 95%CI 1.15–2.35), particularly for SLE (OR 71.87; 95%CI 8.80–586.7), and a higher likelihood of having two or more autoimmune diseases ($p = 0.017$). Increased risk of cardiovascular disorders (OR 1.83; CI 1.32–2.54). Additional analysis by Grover et al. found an elevated risk of venous thromboembolism (OR 3.59, 95%CI 2.17–5.84) in HAE patients
Christiansen et al. 2023[43]	485 HAE-C1INH, 26 HAE-nl-C1INH patients	Significantly higher risk of autoimmune disorders, kidney diseases, anemia, hepatitis, angina, depression and sleep disturbance.
Zanichelli et al. 2024[44]	446 HAE patients; followed up to a 43-year period	A greater prevalence compared with general population for heart diseases (9.6% vs. 4.8%), acute myocardial infarction (5.6% vs. 1.4%), HCV infection (10.5% vs. 2.5%), and appendectomy (15.9% vs. 4.3%).
Perego et al., 2020[35]	1113 Italian HAE patients and their cause of death	Cancer was the most prevalent cause of death, detected in 28 subjects (17 males), in which hepatocarcinoma constituted 19.2% of all malignancies, however with hepatitis C virus infection present in 3 of the 5 patients.
Rahal et al., 2014[91]	Case report	Case report of hepato-cellular carcinoma after long-term use of Danazol for Hereditary Angioedema
Beck et al., 2020[49]	Case report	Accumulation of membrane attack complex in muscle tissue leading to necrotizing myopathy and myositis-like syndrome.

Table 2. Percentage of HAE patients with specific comorbidities, compared with general population; OR and 95%CI (confident interval) included where applicable. Only studies with matched control were listed.

Study/Cohort	Comorbidity	Cases (%)	Controls (%)	OR (95% CI)	*p* value
Sundler et al., 2022[97] Grover et al., 2022[70]	All cardiovascular diseases	22.18%	13.47%	1.83 (1.32–2.54)	< 0.001
	Venous thrombosis/embolus	7.95%	2.01%	4.20 (2.42–7.23)	< 0.001
Case-control study 239 Swedish HAE (type I & II) patients with 2383 matched control	Hypertension	15.06%	9.78%	1.64 (1.12–2.39)	0.01
	All autoimmune diseases	17.6%	11.5%	1.65 (1.15–2.35)	0.01
	Systemic lupus erythematosus	2.9%	0.04%	71.87 (8.80–586.7)	< 0.001
	Cardiovascular diseases	9.6%	4.8%	n/a	n/a
Zanichelli et al. 2024[44] 446 Italian HAE patients	Acute myocardial infarction	5.6%	1.4%	n/a	n/a
	Appendectomy	15.9%	4.3%	n/a	n/a
	HCV infection	10.5%	2.5%	n/a	n/a
Farkas et al (2011)[52] 130 HAE patients matched with non C1-INH deficient control	Immunoregulatory disorders	11.5%	5.2%	n/a	n/a

Early studies researching the link between C1-INH deficiency and autoimmune disease started in the 1980s where researchers investigated circulating ICs in HAE patients; however, did not find any major changes,[47] and the group suggested that ICs accumulation is not a major factor of autoimmunity in patient with C1-INH deficiency. A Kessel et al.[48] conducted an immunologic survey on 61 HAE patients, in which 7 (11.4%) were diagnosed with an immunoregulatory disorder. Their measured autoreactive autoantibodies and extensive assessment on B cell activation phenotypes revealed a marked increase in serum autoantibodies (47.5%), and significant increase in B cell activity with increased expression of TLR-9 (Toll-like receptor 9). In addition, a detailed case report of a HAE patient from Japan demonstrated a significant accumulation of membrane attack complex in muscle tissue leading to necrotizing myopathy and myositis-like syndrome.[49]

Brickman et al.[50,51] studied 157 HAE patients which revealed a significant increase in manifestations of autoimmune disorders. In their cohort 19/157 (12%) patients were found to have either systemic or organ-specific autoimmune disease. Farkas et al (2011)[52] in their study on 130 HAE patients, found that the incidence of immunoregulatory disorders was 11.5%, compared with 5.2% in non-C1-INH-deficient controls. A 2020 study by the same group on a database of 589 C1-INH patients identified 76 patients (12.9%) with coexisting autoimmune disease (AD);[53] furthermore the study noted that HAE patients with C1-INH replacement therapy had a lower number of visits for coexisting ADs compare to patients on other modes of treatment. A single-center study on a Canadian HAE cohort also found a similar rate of autoimmune disorder (6/49 patients, 12.24%).[54] The most recent study (2022) is one population-based cohort in Sweden comparing 239 HAE patients with 2383 matched control, the research found a significant increase in risk of autoimmune diseases (OR 1.65; 95%CI 1.15–2.35), particularly for SLE (OR 71.87; 95%CI 8.80–586.7), and a higher likelihood of having two or more autoimmune diseases ($p = 0.017$).[55]

The challenge in establishing a clear causative relationship between HAE and autoimmune disorders stems from the limited size of available cohorts, inadequate follow-up time, and the absence of definitive experimental evidence. It is suggested from the evidence that the complement perturbation from HAE alone is not enough for the development of autoimmune disorders, but in combination with other factors (genetics, environmental, infection, etc) it would likely contribute to tipping the balance toward autoimmunity. Nevertheless, even with no proven causal relationship, the presence of autoimmune disease in HAE patients could complicate management effort as both conditions would synergize to over-activate and deplete complement components, further worsening disease severity. These data suggest that natural history studies, and laboratory experiments should be conducted to better understand the effect of complement dysregulation and predisposition to autoimmune disorders.

HAE and Malignancy

Bradykinin as well as its 2 receptors (bradykinin B1 and B2 receptor) are known to be involved in cancer pathogenesis through promotion of inflammation, matrix remodeling, angiogenesis and metastasis.[56–59] As an important cellular junction and vascular mediator, bradykinin have been linked to cancer angiogenesis proliferation migration and invasion.[24,25,59] Bradykinin and bradykinin receptor antagonists were considered potential target for anti-cancer agents, however, no clinically trial data are yet available.[60,61] The only clinically available bradykinin receptor antagonist as of now is Icatibant, which is used for acute management of HAE attacks.[62] The short half-life of Icatibant would make it unlikely to be successful in chronic management of malignancies. In separated studies, it is noted that over-expression of bradykinin pathway, glioblastoma (primary brain tumor) can disrupt the blood-brain barrier (BBB) resulting in vasogenic edema.[63,64] Based on this interaction, Naro et al.[65] demonstrated the successful usage of plasma-derived C1-INH to control cerebral edema in patient with glioblastoma, the authors suggested that targeting the contact activation system can be a viable therapeutic strategy for patient with glioblastoma.

Another concern for HAE patients is the complement system perturbation, which has been reported to have a paradoxical effect on tumorgenesis, and cancer treatment responses.[66] Major studies and reviews suggest that increased complement activity, especially within the tumor micro-environment promote tumor development through the modulation of chronic inflammation and inhibition of T-cell responses.[66–68] These data have raised questions over the risk of malignancy in HAE patients and if HAE might worsen the prognosis for cancer.

However, clinical evidence regarding the risk of malignancy in patients with hereditary angioedema (HAE) is limited. Stepaniuk et al.[54] research from a single center in Canada included the retrospective review of the charts of 49 HAE patients that identified six patients with concurrent malignancy diagnosis. Data from a cohort of patients diagnosed with HAE since 1973 sourced from the ITAlian network for C1-INH-HAE in the HAE Global Registry (ClinicalTrials.gov NCT03828279) involved 1113 patients and identified their causes of death. Notably, cancer was the most prevalent cause of death, detected in 28 subjects (17 males), in which hepatocarcinoma constituted 19.2% of all malignancies, however with hepatitis C virus infection present in 3 of the 5 patients.[35] A Swedish cohort study, however, found no increased risk of cancer in HAE patients compared with the control group.[55]

Similar to autoimmune diseases, even with an unclear causal link, the presence of malignancy as a co-morbidity in HAE would significantly complicate management. This is particularly more relevant in the context of cancer treatment as many choices of therapy (surgery, radiotherapy, chemotherapy…) could be a trigger for an HAE attack. Stricter monitoring and use of short term, and possibly long term prophylaxis, is therefore recommended before many of the procedures that may be indicated during cancer therapy.[69]

HAE and Cardiovascular disorder

Epidemiological data have pointed to the relationship between HAE and cardiovascular disorders. The Swedish HAE registry study on comorbidity found an increased risk of cardiovascular disorders (OR 1.83; CI 1.32–2.54) including hypertension, arterial and venous thrombosis in HAE patients.[55] Additional analysis by Steven P et al.[70] found an elevated risk of venous thromboembolism (OR 3.59, 95%CI 2.17–5.84) in HAE patients. Zanichelli et al. (2024)[44] cohort of 446 HAE patients revealed greater prevalence of heart diseases (9.6% vs. 4.8%), acute myocardial infarction (5.6% vs. 1.4%) among HAE patients. Converserly, a recent study by Nebenführer et al.[71] found no evidence of endothelial dysfunction in HAE patients. Christiansen et al. (2023)[43] data from the US Hereditary Angioedema Association revealed a significantly higher risk of angina symptom but lower prevalence of other cardiovascular comorbidities. There have been several other interesting observations: FXII (coagulation factor XII deficiency) is associated with all-cause mortality,[72] ischemic stroke, and myocardial infarction;[73] FXII deficiency has been found in 20% of HAE-nl-C1-INH patients, and can be observed in HAE patient due to overactivation of FXII during attacks.[4,74]

The understanding of mechanism in which HAE would influence the risk of cardiovascular disease is still limited. While the contact system was considered to have no effect on hemostasis, changes to coagulation parameters have also been confirmed clinically in HAE patients and animal models have shown the important role of FXII in thrombosis.[75–77] The most relevant factor that would likely influence the elevated risk of cardiovascular disorder in HAE patient is the dysregulation of the kinin–kallikrein system as bradykinin and bradykinin receptors play an important role in cardiovascular homeostasis.[78] Changes to cellular junction and endothelial permeability caused by bradykinin have also been linked to multiple cardiovascular disorders.[70,71] Bradykinin, a vasoactive peptide, plays a role in modulating vascular tone and inflammation, and its dysregulation can lead to disruptions in cellular and endothelial integrity, thereby inducing the development and progression of cardiovascular diseases.[24]

Currently, the understanding of how Hereditary Angioedema (HAE) relates to cardiovascular disease is limited due to a lack of epidemiological and laboratory data, secondary to being a rare disease. However, recent observations point to a possible link between HAE and cardiovascular disorders.[55,77,79,80] Additional clinical and experimental research is required to better understand and attenuate the long-term cardiovascular risk in HAE patients.

Hereditary angioedema and psychological disorders

It is well established that the burden of illness associated with hereditary disorders greatly affect quality of life and psychological wellness.[81] HAE patients reported a higher incident of anxiety and depression;[82,83] it is believed to stem from the burden of disease, unpredictability of attacks, low quality of life due to work/social impairment, and difficulty in daily activities.[83,84] The advent of modern HAE medication in the US and the EU was followed by a decrease in self-reported severe psychological problem in HAE-C1-INH patient (17% in 2013, down from 53% in 2009).[85]

The literature suggests that these psychological problems stem from the heightened burden of disease and lowered quality of life. However, recent experimental evidence reveal some mechanism tying the psychological aspects itself as an integral component of HAE pathophysiology. Rouhiainen et al.,[86] conducted a series of pharmacological experiment in mice in combination with human genetic association analysis to reveal the role of the bradykinin system in mediating stress responses. The group suggest that changes to the kallikrein-kinin system activity may predispose to stress and anxiety disorder, pointing to the previous genome-wide association study that found bradykinin receptor B2 gene (BDKRB2) to be associated with risk of panic disorder, bipolar disorder and major depression.[87] In an *in vivo* study, Dorit Farfara et al reduced circulating C1-INH in wild-type mice using antisense oligonucleotide to simulate long-term plasma C1-INH deficiency similar to HAE patient.[88] This resulted in the activation of KKS, increased BBB permeability, infiltration of immune cell, and glial cell activation, and the mice exhibit marked cognitive impairment and depressive-like behavior.[88]

Currently, stress is considered as a trigger to HAE attacks, but recent animal research suggests that stress may be a part of the disease pathophysiology, and the stress that often proceeds an attack, which patients perceive as a trigger, may be secondary to increasing levels of circulating bradykinin. More observation and experimental study are required on this topic, but it would likely change how we approach HAE patient with stress, anxiety and other psychological problems. Whether a trigger or a result of bradykinin, referral for psychological evaluation, and consultation should be recommended for HAE patients, since stress and anxiety are common in HAE, and potential use of SSRIs, or similar medication, may optimize quality of life and normalcy.

Comorbidities from treatment-associated adverse effects

Synthetic attenuated androgen (i.e danazol, stanozolol) that is used as a long-term prophylaxis (LTP) of hereditary angioedema. Extended usage of attenuated androgen, especially beyond 10 years, aside from known side effects (virilizing, weight gain, hepatic toxicity, erythrocytosis, hyperlipidemia, and mood disturbances), has been linked to an increased risk of hepato-cellular carcinoma.[89–92] This problem might be more important for older HAE patients as attenuated androgen was the only medication available for long-term prophylaxis up until the recent past. The same problem applies to patients in less developed country where attenuated androgen may be the more affordable therapy for long term prophylaxis.

Since the introduction of more effective prophylactics such as recombinant C1-INH[93,94] plasma-derived C1-INH (IV C1-INH or SC C1-INH),[95] lanadelumab (plasma kallikrein inhibitor),[96] patients have had a wider choice for LTP, thus reduced the demand for anabolic androgen usage. In the US, attenuated androgen use have been relegated to second-line LTP with limited indications for HAE patient. However, previous history of danazol or stanozolol usage should still be concerned and noted to follow for potential long-term side effect.

Concluding remarks

C1-inhibitor (C1-INH) plays a pivotal role in regulating the complement and contact activation pathways, as well has having some influence on the coagulation and fibrinolytic pathways, and thus serves as an early and crucial regulator of homeostasis. Examining the extent of disruption caused by C1-INH deficiency is essential for comprehending its impact on immune surveillance, inflammatory processes and long term health of patients with HAE. This understanding not only holds significance for HAE patients but can promise broader implications for the management, treatment and of other diseases and conditions. These insights serve not only to enhance care for HAE patients, but also to open up the possibility of targeting the C1-INH related pathway as a viable therapeutic strategy for various chronic diseases.

Following our review we feel that annual health survey of patients with HAE should include ESR, CRP, ANA, CBC, CMP and TFT to assess for autoimmune diseases, cancers, and other at risk chronic illnesses. With the use of androgens this assessment should be broadened to include lipid panel, urine chemistry, and liver ultrasounds, preferably every 6 months. Evaluation and management of stress and anxiety should be included as a routine component of care for HAE patients. With additional research, especially with large database assessments, suggestive annual assessments for general health for HAE patients should be altered as more data becomes available and clarifies the degree of additional risks.

Key messages

- Hereditary angioedema (HAE) is a rare hereditary disorder characterized by episodic swelling and life-threatening airway obstruction caused by laryngeal angioedema.
- Recent clinical and experimental studies suggested that the dysregulation of the many pathways involved in HAE may lead to an increase of other pathologies and comorbidities
- Annual health survey of patients with HAE should include ESR, CRP, ANA, CBC, CMP and TFT to assess for autoimmune diseases, cancers, and other chronic illnesses.
- Evaluation and management of stress and anxiety should be included as a routine component of care for HAE patients.

Competing interests

Dr Craig served as a speaker and researcher for Biomarin, CSL-Behring, Intellia, Astria and Takeda; researcher for Ionis, KalVista, and Pharvaris; speaker for Grifols; consultant for Astria, Biocryst, Biomarin, CSL Behring, and Intellia; Director of ACARE International Hereditary Angioedema Center; and member of the Medical Advisory Board for the HAE-A.

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Authors' contributions

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