Study to Adjudicate Hereditary Angioedema with Normal C1INH Diagnoses in the PIONEER-HAE Database

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Background

- People living with hereditary angioedema (HAE) experience unpredictable, painful, and debilitating attacks of tissue swelling that can be life-threatening when involving the larynx[1]
- While HAE is usually categorized by decreased levels (type 1) or function (type 2) of C1-esterase inhibitor (C1INH), a substantial proportion of patients with phenotypical angioedema have both normal levels and function of C1INH (nC1INH), and are designated as HAE-nC1INH[2]
- Most patients diagnosed with HAE-nC1INH do not carry a genetic marker associated with the disease[1]
- The lack of standardized diagnostic approaches for HAE-nC1INH makes accurate diagnosis challenging[2]; thus, further elucidation of clinical diagnostic practices is warranted

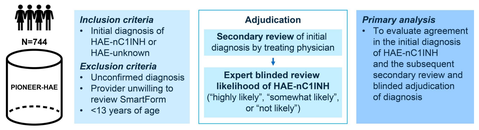
Objective

- To understand how community-based allergists/immunologists approach diagnosis of HAE-nC1INH

Methods

- Data from patients diagnosed with HAE-nC1INH or HAE-unknown (cut-off date: March 1, 2024) from the Patient-Important Outcomes Data Repository[3] (PIONEER-HAE; N=744) underwent secondary review by treating physicians to adjudicate diagnosis, and subsequent adjudication by 2 blinded HAE experts (**Figure 1**)

Figure 1. Study design



HAE, hereditary angioedema; nC1INH, normal C1-esterase inhibitor; PIONEER, Patient-Important Outcomes Data Repository.

- Secondary review of HAE type by treating physician was assessed via a SmartForm questionnaire, which was designed by immunology experts and based on published consensus clinical criteria for HAE-nC1INH,[4] to capture the most important clinical presentation data utilized in diagnosis (**Table 1**)
- Assignment of "highly likely", "somewhat likely", or "not likely" HAE-nC1INH was based on the clinical guideline criteria[5] (**Table 2**)

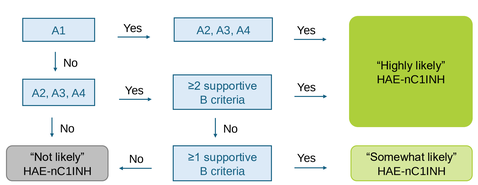
Table 1. Key parameters collected

Patient history
Family history of angioedema, angioedema without urticaria, year of symptom onset
Genetic or laboratory testing
Normal or near-normal C4 level and C1 inhibitor antigen level and function
Mutation in *F12*, *PLG*, *ANGPT1*, *KNG-1*, *MYOF*, or *HS3ST6*
SERPING1 mutation
Clinical history and treatment response
Use of HAE medication (prophylactic or rescue; responsiveness)
Rapid and durable response to a bradykinin-targeted medication
Use of antihistamine/corticosteroid (prophylactic or rescue; responsiveness)
Angioedema attack information (location, medication, resolution, prodromal symptoms, attack triggers)
• For abdominal attacks: (a) Does this patient experience swelling exclusively in the abdominal region? (b) Have you conducted/ordered imaging of the patient's abdomen to rule out potential gastrointestinal causes?
Secondary diagnosis review
Initial diagnosis of HAE type (HAE-nC1INH or HAE-unknown)
• As the physician providing care for this patient, do you agree that this is the most appropriate diagnosis subtype for the patient?

HAE, hereditary angioedema; nC1INH, normal c1-esterase inhibitor.

Table 2. HAE-nC1INH diagnosis assignment criteria[5]

Consensus criteria (A)	
A1	Known genetic mutation Family history of angioedema
A2	History of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema
A3	Normal or near-normal C4 level and C1 inhibitor antigen level and function
A4	Documented lack of response to high-dose antihistamines
Supportive criteria (B)	
B1	History of no response to epinephrine and glucocorticoids
B2	History of prompt and durable responses to a bradykinin-targeted medication
B3	Documented, visible angioedema or, in patients with predominantly abdominal symptoms, evidence of bowel-wall edema identified



HAE, hereditary angioedema; nC1INH, normal c1-esterase inhibitor.

Results

Patients

- 147 patients from the PIONEER-HAE database (N=744) had a provider diagnosis of HAE-nC1INH or HAE-unknown
  - 7 patients were excluded from the analysis[a]
- The majority of the study population (N=140) was female (121/140; 86%) and White (95/116; 82%)
  - Most patients (117/140; 84%) were initially diagnosed with HAE-nC1INH and 16% (23/140) were diagnosed with HAE-unknown
  - After secondary review by treating physicians, 117 (84%) patients were classified as HAE-nC1INH (from 113 initially diagnosed HAE-nC1INH; 4 HAE-unknown), 21 (15%) HAE-unknown, and 2 (1%) C1-inhibitor-deficient HAE
- There was 93% (130/140) alignment between initial diagnosis and secondary review by the treating physician (**Table 3**; **Figure 2**)

[a]Secondary SmartForm review missing, n=1; HAE not confirmed, n=2; <13 years of age, n=4

Blinded adjudication of HAE diagnosis

- Of 140 patients classified as HAE-nC1INH or HAE-unknown: 28 (20%) patients were determined as "highly likely" to have HAE-nC1INH, 15 (11%) patients were "somewhat likely" and 32 (23%) patients were deemed "not likely" to have HAE-nC1INH (**Table 3**)
  - 65 (46%) patients lacked sufficient information to confirm or exclude a diagnosis of HAE-nC1INH (**Figure 2**)

Table 3. Adjudication of initial HAE diagnosis

HAE classification by treating physician		Expert blinded review likelihood of HAE-nC1INH, n/n (%)					
Initial diagnosis	n	Secondary review	n (%)	Highly likely	Somewhat likely	Not likely	Insufficient data
HAE-nC1INH	117	HAE-nC1INH	113 (96.6)	28/113 (24.8)	13/113 (11.5)	23/113 (20.4)	49/113 (43.4)
		HAE-unknown	4 (3.4)	–	–	3/4 (75.0)	1/4 (25.0)
Subtotal	*117*			*28/117 (23.9)*	*13/117 (11.1)*	*26/117 (22.2)*	*50/117 (42.7)*
HAE-unknown	23	HAE-unknown	17 (73.9)	–	1/17 (5.9)	3/17 (17.6)	13/17 (76.5)
		HAE-nC1INH	4 (17.4)	–	1/4 (25.0)	1/4 (25.0)	2/4 (50.0)
		Type 1 HAE	2 (8.7)	–	–	2/2 (100)	–
Subtotal	*23*			–	*2/23 (8.7)*	*6/23 (26.1)*	*15/23 (65.2)*
Total, n (%)	140			28/140 (20.0)	15/140 (10.7)	32/140 (22.9)	65/140 (46.4)

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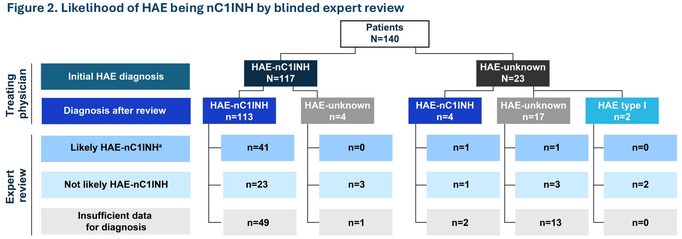
Figure 2. Likelihood of HAE being nC1INH by blinded expert review



HAE, hereditary angioedema; nC1INH, normal C1-esterase inhibitor.
[a]Likely HAE-nC1INH combines both "highly likely" and "somewhat likely" for HAE-nC1INH.

Alignment between secondary review by treating physician and blinded expert review

- Only 36% (42/117) of patients with an HAE-nC1INH diagnosis by secondary review of the treating physician had an expert review diagnosis of "somewhat likely" (12%; 14/117) or "highly likely" for HAE-nC1INH (28/117; 24%)
- This discrepancy is largely due to the proportion of patients with an HAE-nC1INH diagnosis after secondary review (**Table 3**) who had insufficient data for categorization by expert blinded review (**Figure 2**)
- The remaining 24 patients (20.5%; 24/117) were recategorized from HAE-nC1INH to "not likely" after the expert blinded review
- Availability of diagnostic criteria in patients with insufficient data is summarized in **Table 4**

Table 4. Insufficient data for HAE diagnosis based on assignment criteria (n=65)

Consensus criteria (A)		Availability of criteria, n (%)
A1	Known genetic mutation (*F12*, *PLG*, *ANGPT1*, or *KNG-1*)	39 (60)
	Family history of angioedema	65 (100)
A2	History of recurrent angioedema in the absence of concomitant urticaria ***or*** use of a medication known to cause angioedema	55 (85)
A3	Normal or near-normal C4 level and C1 inhibitor antigen level and function	44 (38)
A4	Documented lack of response to high-dose antihistamines	10 (15)
Yes, to A2, A3, and A4		2 (3)
Supportive criteria (B)		
B1	History of no response to epinephrine and glucocorticoids	8 (12)
B2	History of prompt and durable responses to a bradykinin-targeted medication	37 (57)
B3	Documented, visible angioedema ***or*** predominantly abdominal symptoms plus evidence of bowel-wall edema identified	28 (43)

Prevalence of HAE-nC1INH

- Of the patients in the PIONEER-HAE registry, 19% (140/744) were diagnosed with HAE-nC1INH or HAE-unknown
  - After expert review, 31% (43/140) of these patients were "highly likely" or "somewhat likely" for HAE-nC1INH
- Overall, 5.8% (43/744) of the total patients in the PIONEER-HAE registry were "highly likely" or "somewhat likely" for HAE-nC1INH after adjudication

Limitations

- The study is observational in nature and limited by the accuracy and completeness of data provided in the PIONEER-HAE database; it is a limited sample of patients with HAE treated at specific centers in the USA and thus, may not be representative of all patients with HAE

Table 5. Demographic characteristics by likelihood of HAE-nC1INH

Patients	Likely[a] HAE-nC1INH (n=43)	Not likely HAE-nC1INH (n=32)	Insufficient data (n=65)	Total study population (N=140)
Age, years, n (%)				
13–17	1 (2)	1 (3)	1 (2)	3 (2)
18–35	12 (28)	11 (34)	17 (26)	40 (29)
36–50	14 (33)	12 (38)	21 (32)	47 (34)
51–64	9 (21)	6 (19)	18 (28)	33 (24)
65–74	4 (9)	2 (6)	5 (8)	11 (8)
75+	3 (7)	0	3 (5)	6 (4)
Age, mean ± SD	45.8 ± 16.9	41.8 ± 14.4	45.9 ± 15.5	45.0 ± 15.7
Sex, n (%)				
Female	36 (84)	30 (94)	55 (85)	121 (86)
Race, n (%)				
Black	9 (21)	3 (9)	6 (9)	18 (13)
White	30 (70)	20 (63)	45 (69)	95 (68)
Other	0	0	3 (5)	3 (2)
Unknown	4 (9)	9 (28)	11 (17)	24 (17)
Ethnicity, n (%)				
Hispanic or Latino	4 (9)	3 (9)	3 (5)	10 (7)
Not Hispanic or Latino	30 (70)	23 (72)	46 (71)	99 (71)
Unknown	9 (21)	6 (19)	16 (25)	31 (22)
Region, n (%)				
Midwest	6 (14)	6 (19)	27 (42)	39 (28)
Northeast	1 (2)	1 (3)	2 (3)	4 (3)
South	28 (65)	16 (50)	24 (37)	68 (49)
West	8 (19)	9 (28)	12 (18)	29 (21)

HAE, hereditary angioedema; nC1INH, normal c1-esterase inhibitor; SD, standard deviation.
[a]Likely HAE-nC1INH combines both "highly likely" and "somewhat likely" for HAE-nC1INH.

Conclusions

- **In PIONEER-HAE, 19% of patients (>13 years of age) had a diagnosis of HAE-nC1INH or HAE-unknown, suggesting these diagnoses are common with isolated recurrent angioedema**
- **Approximately two-thirds of patients had inadequate documentation of HAE-nC1INH clinical/laboratory criteria, which may reflect limitations of medical record review and/or variability in diagnostic criteria used by specialists in clinical practice**
  - **After adjudication, 5.8% (43/744) of the total patients in the PIONEER-HAE registry were "highly likely" or "somewhat likely" for HAE-nC1INH**
- **These results suggest standardized clinical assessments and validated diagnostic biomarkers are needed to address challenges in HAE-nC1INH diagnosis**

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