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Misdiagnosis trends in patients with hereditary angioedema from the real-world clinical setting

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ABSTRACT

Background: Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) causes swelling in the skin and upper airways and pain in the abdomen because of mucosal swelling. C1-INH-HAE is frequently misdiagnosed, leading to delays in diagnosis, inadequate treatment, and unnecessary procedures.
Objective: To evaluate the history of misdiagnosis in patients participating in the Icatibant Outcome Survey (IOS).
Methods: The IOS is an observational study in which safety and effectiveness of icatibant have been evaluated since 2009. As part of the IOS, patients record any misdiagnoses received before being diagnosed as having C1-INH-HAE.
Results: In January 2016, a total of 418 of 633 IOS patients with C1-INH-HAE type I or II had provided misdiagnosis data. Of these, 185 of 418 (44.3%) received 1 or more prior misdiagnoses. The most common misdiagnoses were allergic angioedema (103 of 185) and appendicitis (50 of 185). A variety of other misdiagnoses were reported, including a substantial number of gastrointestinal disorders (excluding appendicitis). Misdiagnosis rates were similar between males (41.1%) and females (46.5%) and between C1-INH-HAE type I (43.7%) and type II (51.6%). Patients with family members diagnosed as having C1-INH-HAE were significantly less likely to be misdiagnosed than patients without a family history (140 of 366 [41.7%] vs 38 of 58 [65.5%], respectively; $P = .001$). Patients with a prior misdiagnosis had longer median delay to C1-INH-HAE diagnosis (13.3 years) than patients without (1.7 years; $P < .001$).
Conclusion: From this large database, approximately 50% of patients with C1-INH-HAE type I or II have previously had their conditions misdiagnosed, most commonly as allergic angioedema or appendicitis. Misdiagnosis results in marked delays in receiving the correct diagnosis, during which time patients cannot access effective, lifesaving treatment.
Trial Registration: ClinicalTrials.gov: NCT01034969.

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Introduction

Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant condition that causes recurrent episodic edema without wheals of the skin, abdomen, and upper airways, which can lead to fatal obstruction.[1–6] Two phenotypic variants of C1-INH-HAE have been described: type I, in which antigenic and functional plasma C1-INH levels are below normal range, and type II, in which antigenic C1-INH levels are normal but functional C1-INH levels are below normal.[4] This disease is estimated to occur in approximately 1 in 50,000 individuals worldwide. C1-INH-HAE has substantial variability in disease manifestations, and symptoms such as swelling and pain can overlap with other more common allergic and gastrointestinal conditions. A low clinical suspicion for C1-INH-HAE, particularly among physicians not familiar with C1-INH-HAE, can lead to misdiagnosis.[3,7–10] Incorrect diagnoses range from allergies to systemic lupus erythematosus, with a variety of treatments, including antihistamines, corticosteroids, and other immunosuppressive therapies,[7,11–13] which can have adverse effects and are of limited clinical utility.[6,12,14–17] Patients with C1-INH-HAE typically experience more than a 10-year delay in diagnosis,[11] and delays in reaching a correct diagnosis can have significant consequences for the patient, particularly if the edema involves the laryngeal tissues with an associated increased risk of suffocation.[6]

The issue of misdiagnosis and its consequences has been previously explored in case studies, post hoc medical record reviews, and country-specific patient registries.[11,12,14,16] To better characterize this issue, the clinical aspects and trends of C1-INH-HAE misdiagnosis need to be investigated within a large, diverse, multinational, real-world patient population. The Icatibant Outcome Survey (IOS) (ClinicalTrials.gov Identifier: NCT01034969) is an ongoing, Shire-sponsored, international, prospective, observational registry that collects demographic, medical history, and clinical outcomes data in patients eligible for treatment with icatibant, a subcutaneously administered bradykinin B2 receptor antagonist, in the treatment of C1-INH-HAE.[18,19] Analyses of data from patients participating in the IOS were conducted to help determine trends in C1-INH-HAE misdiagnosis.

Methods

The IOS observational registry, initiated in 2009, is being conducted at 50 participating sites in 11 countries (Austria, Brazil, Denmark, France, Germany, Greece, Israel, Italy, Spain, Sweden, and the United Kingdom) to monitor the safety and effectiveness of icatibant. All patients provide written informed consent before participating in the IOS, and each participating study site operates in accordance with local ethics committees and/or health authorities, the Declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice guidelines.

Patients with a diagnosis of C1-INH-HAE (type I or II), clinically confirmed by laboratory tests (C1-INH concentration and function), who were receiving or were a candidate for icatibant treatment were included in this analysis. Patients attended regular follow-up visits, recommended every 6 months according to physician routine clinical practice. Data were collected from electronic forms completed by physicians during routine patient visits. Additional details of the IOS registry have been previously described.[20]

At enrollment, patients reported any misdiagnoses (based on HAE symptoms) received before the diagnosis of C1-INH-HAE. Descriptive retrospective analyses of any reported misdiagnosis were performed using the IOS data collected from July 2009 to January 2016. Descriptive statistics were used to compare patients who had 1 or more misdiagnoses with patients who had no misdiagnoses. Statistical testing was considered exploratory in this observational study and no adjustment for multiplicity was performed. Patients with a previous misdiagnosis also were compared by type of misdiagnosis, C1-INH-HAE type I or II, sex distribution, and familial history of C1-INH-HAE using descriptive statistics. The Wilcoxon-Mann-Whitney test was used to compare continuous variables. A χ^2 test was used for comparisons between categories, with a statistical significance level of $\alpha = 0.05$.

Results

Frequent Misdiagnosis of C1-INH-HAE

As of January 2016, a total of 633 patients with C1-INH-HAE (type I or II) were enrolled in the IOS. Of these, 418 patients (66.0%) had provided misdiagnosis data. Almost half of these patients (185 of 418 [44.3%]) had received 1 or more misdiagnoses before being diagnosed as having C1-INH-HAE, whereas 223 of 418 (55.7%) had never had a misdiagnosis. Patients with and without a prior misdiagnosis had similar demographics for sex, C1-INH-HAE diagnosis (type I or II), ethnicity, and age at symptom onset (Table 1). Patients with 1 or more misdiagnoses were significantly older at the time of correct diagnosis (median age, 28.4 years; range, 3.8–77.3 years) than those without a misdiagnosis (median age, 16.7 years; range, 0.0–77.3 years; $P < .001$). Patients with family members with C1-INH-HAE were significantly less likely to receive an initial misdiagnosis compared with those without familial C1-INH-HAE (140 of 336 [41.6%] vs 38 of 58 [65.5%]; $P < .001$) (Table 2). The overall country-specific rate of C1-INH-HAE misdiagnosis from IOS patients is given in Table 3,

Table 1
Patient Characteristics in Those With and Without a Prior HAE Misdiagnosis

Characteristic	Patients with ≥1 misdiagnoses (n = 185)	Patients without a misdiagnosis (n = 233)
Age at enrollment, mean (SD) [range], y	43.4 (14.2) [1.0–81.6]	38.5 (15.2) [1.0–81.8]
Female, No. (%)	113 (61.1)	130 (55.8)
Ethnicity, No. (%)[a]		
White	174 (95.1)	220 (95.7)
Asian	5 (2.7)	4 (1.7)
Other	4 (2.2)	6 (2.6)
C1-INH-HAE diagnosis, No. (%)		
Type I	169 (91.4)	218 (93.6)
Type II	16 (8.6)	15 (6.4)
Age at symptom onset, mean (SD) [range], y[b]	14.0 (11.2) [0.1–67.0]	12.9 (11.8) [0.3–77.0]
Age at diagnosis, mean (SD) [range], y[c]	29.0 (14.7) [3.8–77.3]	20.4 (15.7) [0–77.3]
Time from symptom onset to C1-INH-HAE diagnosis, mean (SD) [median], y[d]	15.0 (13.4) [13.3]	7.0 (13.2) [1.7]
No. of attacks per year, mean (SD) [median]	18.9 (21.2) [10.7]	18.9 (27.6) [7.2]
Frequency of attacks per year, No. (%)[e]		
<10 attacks per year	82 (48.8)	123 (56.7)
≥10 attacks per year	86 (51.2)	94 (43.3)

Abbreviations: C1-INH-HAE, hereditary angioedema due to C1 inhibitor deficiency; HAE, hereditary angioedema.
[a]Data reported for 183 patients with 1 or more misdiagnoses and 230 patients without a misdiagnosis.
[b]Data reported for 177 patients with 1 or more misdiagnoses and 204 patients without a misdiagnosis.
[c]Data reported for 183 patients with 1 or more misdiagnoses and 220 patients without a misdiagnosis.
[d]Data reported for 176 patients with 1 or more misdiagnoses and 198 patients without a misdiagnosis.
[e]Data reported for 168 patients with 1 or more misdiagnoses and 217 patients without a misdiagnosis.

Table 2
Patient Misdiagnosis by Family History of HAE

Previous misdiagnosis	No. (%) of patients with family history of HAE	
	Yes	No
Yes	140 (41.7)	38 (65.5)
No	196 (58.3)	20 (34.5)
Total[a]	336	58

Abbreviation: HAE, hereditary angioedema.
[a]Data available for both family history and misdiagnosis; missing or unknown data were excluded.

and C1-INH-HAE misdiagnosis by decade of patient birth is given in Table 4.

Allergic Angioedema and Appendicitis Misdiagnoses

In patients who reported 1 or more misdiagnoses (Fig 1), the most common diagnoses were allergic angioedema (103 of 185 [55.7%]) and appendicitis (50 of 185 [27.0%]). Misdiagnoses were reported by 169 of 387 patients with C1-INH-HAE type I (43.7%) and by 16 of 31 patients with type II (51.6%) ($P = .39$). The percentage of patients reporting each misdiagnosis type was similar between both C1-INH-HAE types (Fig 2).

The percentages of patients who reported 1 or more misdiagnoses were not statistically different between males (72 of 175 [41.1%]) and females (113 of 243 [46.5%]) ($P = .28$). Similarly, the types of misdiagnosis were not different between males and females (Fig 3).

Substantial Delays in Receiving the Correct Diagnosis

Patients with C1-INH-HAE who had a prior misdiagnosis experienced a significantly longer delay from symptom onset to C1-INH-HAE diagnosis (median, 13.3 years; range, −13.5 to 67.3 years) than patients without (median, 1.7 years; range, −41.8 to 66.9 years; $P < .001$). Misdiagnoses of nonallergic angioedema and biliary disorder resulted in the greatest mean time from symptoms to C1-INH-HAE diagnosis (Table 5).

Discussion

This study found that patients with C1-INH-HAE commonly receive misdiagnoses, frequently allergic angioedema or appendicitis. The present analysis is the first using IOS data to show that an initial misdiagnosis is a major driver of the long delays that patients

Table 3
Country-Specific Rate of C1-INH-HAE Misdiagnosis From IOS Patients[a]

IOS country	No. (%) of patients with ≥1 misdiagnoses (n = 185)	No. (%) of patients without a misdiagnosis (n = 233)
Austria	11 (84.6)	2 (15.4)
Brazil	16 (84.2)	3 (15.8)
Denmark	15 (68.2)	7 (31.8)
Greece	12 (63.2)	7 (36.8)
Italy	28 (46.7)	32 (53.3)
United Kingdom	26 (46.4)	30 (53.6)
Israel	22 (41.5)	31 (58.5)
Germany	27 (35.5)	49 (64.5)
France	6 (28.6)	15 (71.4)
Spain	22 (28.6)	55 (71.4)
Sweden	0 (0.0)	2 (100.0)

Abbreviations: C1-INH-HAE, hereditary angioedema due to C1 inhibitor deficiency; IOS, Icatibant Outcome Survey.
[a]The numbers of patients by country with missing misdiagnosis data are as follows: France, n = 182; Germany, n = 11; United Kingdom, n = 8; Spain, n = 7; Israel, n = 4; Denmark, n = 2; and Italy, n = 1.

Table 4
Misdiagnosis by Decade of Birth[a]

IOS country	Year of birth															
	<1950		1950–1959		1960–1969		1970–1979		1980–1989		>1990					
	No. (%) of patients with ≥1 misdiagnoses (n = 20)	No. (%) of patients without a misdiagnosis (n = 20)	No. (%) of patients with ≥1 misdiagnoses (n = 27)	No. (%) of patients without a misdiagnosis (n = 28)	No. (%) of patients with ≥1 misdiagnoses (n = 54)	No. (%) of patients without a misdiagnosis (n = 42)	No. (%) of patients with ≥1 misdiagnoses (n = 41)	No. (%) of patients without a misdiagnosis (n = 57)	No. (%) of patients with ≥1 misdiagnoses (n = 36)	No. (%) of patients without a misdiagnosis (n = 54)	No. (%) of patients with ≥1 misdiagnoses (n = 7)	No. (%) of patients without a misdiagnosis (n = 32)				
Austria	2 (10.0)		5 (18.5)		1 (1.9)		2 (4.9)	2 (3.5)	1 (2.8)							
Brazil	1 (5.0)	1 (5.0)	1 (3.7)		6 (11.1)		5 (12.2)	1 (1.8)	3 (8.3)			1 (3.1)				
Denmark	1 (5.0)		2 (7.4)		7 (13.0)	2 (4.8)	2 (4.9)	3 (5.3)	2 (5.6)	2 (3.7)	1 (14.3)					
Greece	1 (5.0)		2 (7.4)		1 (1.9)		3 (7.3)	3 (5.3)	3 (8.3)	1 (1.9)	2 (28.6)	3 (9.4)				
Italy	4 (20.0)	3 (15.0)	2 (7.4)	3 (10.7)	10 (18.5)	5 (11.9)	9 (22.0)	6 (10.5)	2 (5.6)	6 (11.1)	1 (14.3)	9 (28.1)				
United Kingdom	1 (5.0)	3 (15.0)	3 (11.1)	5 (17.9)	11 (20.4)	8 (19.0)	3 (7.3)	4 (7.0)	6 (16.7)	8 (14.8)	2 (28.6)	2 (6.3)				
Israel	3 (15.0)	2 (10.0)	3 (11.1)	2 (7.1)	6 (11.1)	3 (7.1)	5 (12.2)	10 (17.5)	5 (13.9)	8 (14.8)		6 (18.8)				
Germany	2 (10.0)	7 (35.0)	4 (14.8)	9 (32.1)	6 (11.1)	12 (28.6)	6 (14.6)	6 (10.5)	8 (22.2)	12 (22.2)	1 (14.3)	3 (9.4)				
France			2 (7.4)		1 (1.9)	2 (4.8)	1 (2.4)	6 (10.5)	2 (5.6)	4 (7.4)		3 (9.4)				
Spain	5 (25.0)	4 (20.0)	3 (11.1)	9 (32.1)	5 (9.3)	9 (21.4)	5 (12.2)	16 (28.1)	4 (11.1)	13 (24.1)		4 (12.5)				
Sweden						1 (2.4)						1 (3.1)				
Overall by decade of birth, %	**50.0**	**50.0**	**49.1**	**50.9**	**56.2**	**43.8**	**41.8**	**58.2**	**40.0**	**60.0**	**17.9**	**82.1**				

Abbreviation: IOS, Icatibant Outcome Survey.
[a]The numbers of patients by country with missing misdiagnosis data are as follows: France, n = 182; Germany, n = 11; United Kingdom, n = 8; Spain, n = 7; Israel, n = 4; Denmark, n = 2; and Italy, n = 1.

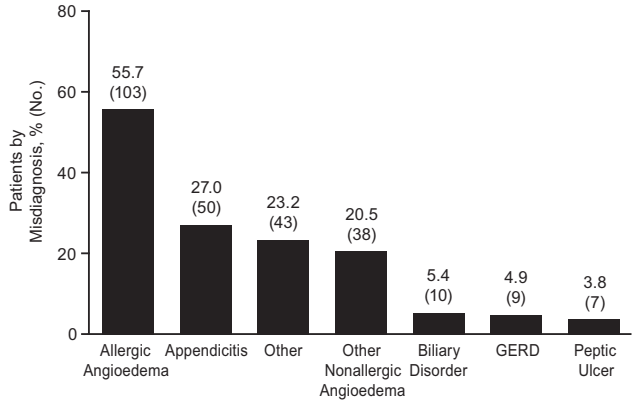

Figure 1. Percentage of patients with hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) by misdiagnosis (n = 185). Patients may have reported more than 1 misdiagnosis. For other misdiagnoses, see Table 5. GERD indicates gastroesophageal reflux disease.

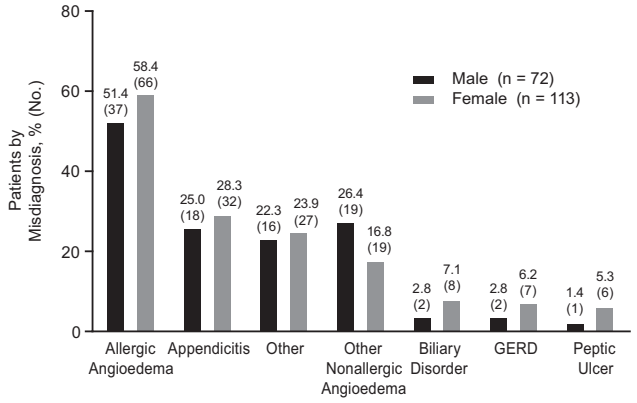

Figure 3. Percentage of patients with hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) by misdiagnosis according to sex. Patients may have reported more than 1 misdiagnosis. For other misdiagnoses, see Table 5. GERD indicates gastroesophageal reflux disease.

with C1-INH-HAE can experience before a correct diagnosis of C1-INH-HAE is made.

It is well recognized that patients with C1-INH-HAE can be subject to an initial misdiagnosis, but analyses of misdiagnosis patterns and trends in a real-world setting are scarce.[4,5] The rarity of C1-INH-HAE, heterogeneity of its affected population, and the overlap in symptoms with other more common diseases, such as allergic angioedema and appendicitis, make diagnosing C1-INH-HAE challenging.[3,7–9] Moreover, angioedema is a widely variable disease with different types and subtypes, including acquired angioedema and idiopathic histaminergic angioedema.[4,5] It is understandable, therefore, that clinical suspicion for C1-INH-HAE may be low, particularly among physicians who are not familiar with the disorder or its clinical management.

Our findings suggest that C1-INH-HAE misdiagnoses are not influenced by patient sex or HAE type (I vs II). A numerically higher percentage of males were diagnosed as having other nonallergic angioedema ($P = .12$); however, the broad range of misdiagnoses in this category and the relatively small number of patients prevent any substantial conclusions by sex. Patients with a family history of C1-INH-HAE were significantly less likely to receive misdiagnoses, most likely because of consideration of positive family history in the differential diagnosis. Physician awareness that in 25% of C1-INH-HAE cases there is no positive family history may help decrease misdiagnoses.[21] Nevertheless, it is remarkable that almost half of patients with a family history of C1-INH-HAE received misdiagnoses. This finding could represent an opportunity to improve diagnosis by encouraging family members to come forward for diagnosis and by facilitating diagnosis by primary care physicians. Geographic region could potentially play a part in misdiagnosis rates, although similarly, the small number of patients with misdiagnosis data in each of the 11 countries precludes meaningful comparison.

Patients with C1-INH-HAE may present with abdominal pain, which is reflected in the range of gastrointestinal diagnoses patients in the current study report as being their initial diagnosis. Importantly, angioedema that affects viscera or bowel is not necessarily associated with visible swelling, making a high index of suspicion and careful history taking that includes questions about peripheral or laryngeal swelling essential for a diagnosis of angioedema.[16,22]

In addition, patients with 1 or more misdiagnoses experienced a significantly longer delay that those without a misdiagnosis before receiving a correct C1-INH-HAE diagnosis. A 2013 analysis of IOS data found a median diagnostic delay in patients with C1-INH-HAE type I or II across 8 European countries of 8.5 years (range, 0–62.0 years)[8]; however, that analysis, unlike the present study, did not account for prior misdiagnosis. Given that the age of symptom onset in the present study is similar in both groups and those who

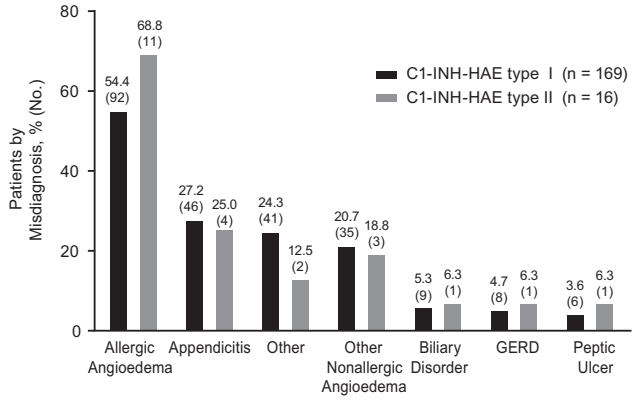

Figure 2. Percentage of patients with hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) by misdiagnosis according to C1-INH-HAE type I or II. Patients may have reported more than 1 misdiagnosis. For other misdiagnoses, see Table 5. GERD indicates gastroesophageal reflux disease.

Table 5
Time (in Years) From First Symptoms to C1-INH-HAE Diagnosis by Type of Prior Misdiagnosis in 185 Patients

Prior misdiagnosis	Time from first symptoms to misdiagnosis, y	
	Mean (SD)	Median (range)
Allergic angioedema (n = 97)	15.5 (13.9)	14.8 (−13.5 to 67.3)
Appendicitis (n = 47)	13.3 (13.8)	12.0 (−1.2 to 67.3)
Other[a] (n = 40)	15.1 (12.0)	13.3 (−0.4 to 46.2)
Nonallergic angioedema (n = 38)	18.0 (14.0)	15.7 (−1.2 to 56.6)
Biliary disorder (n = 10)	16.0 (10.9)	15.8 (0.0 to 34.4)
GERD (n = 8)	16.1 (11.1)	14.4 (−0.4 to 34.4)
Peptic ulcer (n = 7)	18.2 (19.7)	13.4 (−0.4 to 54.0)

Abbreviations: C1-INH-HAE, hereditary angioedema due to C1 inhibitor deficiency; GERD, gastroesophageal reflux disease.
[a]Other diagnoses as reported by patients include colic, colic (gastroenteritis), edema after trauma, endometriosis, familial Mediterranean fever, indigestion, leukemia, rheuma, tonsillitis, urinary tract infection, urticaria, acetonemic vomiting, allergy, bowel obstruction, cardia/neoplasia, colitis, constipation, diverticulitis, dubious fluid in abdomen, gastroenteritis, heartburn, *Helicobacter pylori*, irritable bowel disease, irritable colon, kidney problem, orchitis (acute gastroenteritis), pancreatitis, psychological overstress syndrome, skin and kidney disorder, stress (acute gastroenteritis), and urticaria (tonsillitis). Patients could have reported more than 1 misdiagnosis.

had a misdiagnosis tended to be older when C1-INH-HAE was correctly diagnosed, this delay can be attributed to the initial misdiagnosis. An initial misdiagnosis can have practical consequences for patients with C1-INH-HAE that can range from increased risk of death from laryngeal edema[6] to altering the treatment approach of subsequent health care professionals, delay of effective therapy, and prolonged issues associated with an otherwise manageable condition. Patients with misdiagnoses included those with frequent attacks. Given the age at onset of symptoms, delay in diagnosis is likely to lead to severe disruption of education and early working life and may account for many of the economic, social, and psychological consequences of C1-INH-HAE described elsewhere.[23–27] In a recent study by Bygum et al,[24] misdiagnosis was mentioned by patients as an important burden of their disease and was included in a conceptual model of C1-INH-HAE burden in patients.

Considering that published data regarding C1-INH-HAE misdiagnosis are scarce and consist largely of case reports and country-specific analyses, the relatively large real-world multinational database used in this analysis substantially contributes to the understanding of this issue. Limitations of this analysis necessarily include those related to patient recall, the number of patients analyzed, and the fact that the IOS currently includes only patients from centers in Europe, South America, and the Middle East. Recent evidence from Japan, however, suggests that patients with HAE in non-IOS countries also experience long delays in diagnosis and similar rates of misdiagnosis.[28]

Awareness of C1-INH-HAE has increased in recent years; however, patients continue to experience misdiagnoses, resulting in unnecessary treatment, delays in appropriate diagnosis and therapy, and increased risk of death.[6] Increased awareness of C1-INH-HAE signs, symptoms, and prodromes,[29] the types of common C1-INH-HAE misdiagnoses, knowledge of C1-INH-HAE occurrence in the absence of a positive family history, and wide availability of C4 blood test screening, with C1-INH testing if suspicion is high, may assist physicians and patients in recognizing C1-INH-HAE as a possible cause of symptoms and encourage testing to confirm or rule out C1-INH-HAE. Ongoing education for physicians who are most likely to encounter patients with C1-INH-HAE may reduce misdiagnosis and the delay in receiving a correct diagnosis and treatment.

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References

[1] Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004; 114(suppl 3):S51–S131.

[2] Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119:267–274.

[3] Craig T, Aygören-Pürsün E, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J*. 2012;5:182–199.

[4] Cicardi M, Aberer W, Banerji A, et al; HAWK under the patronage of EAACI (European Academy of Allergy and Clinical Immunology). Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69: 602–616.

[5] Lumry WR. Overview of epidemiology, pathophysiology, and disease progression in hereditary angioedema. *Am J Manag Care*. 2013;19(suppl 7): S103–S110.

[6] Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130: 692–697.

[7] Roche O, Blanch A, Caballero T, Sastre N, Callejo D, López-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol*. 2005;94: 498–503.

[8] Zanichelli A, Magerl M, Longhurst H, Fabien V, Maurer M. Hereditary angioedema with C1 inhibitor deficiency: delay in diagnosis in Europe. *Allergy Asthma Clin Immunol*. 2013;9:29.

[9] Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? *Ann Allergy Asthma Immunol*. 2010;104: 211–214.

[10] Zanichelli A, Arcoleo F, Barca MP, et al. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis*. 2015; 10:11.

[11] Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009;161:1153–1158.

[12] Harten P, Korbacher D, Renk C, Euler HH, Loffler H. Hereditary angioedema. Diagnostic and treatment errors as systemic lupus erythematosus [in German]. *Med Klin (Munich)*. 1999;94:339–344.

[13] Jacobs J. Recurrent attacks of hereditary angioedema: a case of delayed diagnosis. *Allergy Asthma Proc*. 2011;32(suppl 1):S23–S26.

[14] Gompels MM, Lock RJ, Unsworth DJ, Johnston SL, Archer CB, Davies SV. Misdiagnosis of hereditary angio-oedema type 1 and type 2. *Br J Dermatol*. 2003;148:719–723.

[15] Jalaj S, Scolapio JS. Gastrointestinal manifestations, diagnosis, and management of hereditary angioedema. *J Clin Gastroenterol*. 2013;47:817–823.

[16] Nzeako UC. Diagnosis and management of angioedema with abdominal involvement: a gastroenterology perspective. *World J Gastroenterol*. 2010;16: 4913–4921.

[17] Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc*. 2000;75: 349–354.

[18] Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010;363:532–541.

[19] Maurer M, Longhurst HJ, Fabien V, Li HH, Lumry WR. Treatment of hereditary angioedema with icatibant: efficacy in clinical trials versus effectiveness in the real-world setting. *Allergy Asthma Proc*. 2014;35:377–381.

[20] Maurer M, Aberer W, Bouillet L, et al; I. O. S. Investigators. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. *PLoS One*. 2013;8:e53773.

[21] Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the *C1inhibitor* gene of patients with angioedema. *J Allergy Clin Immunol*. 2000;106:1147–1154.

[22] Nzeako UC, Longhurst HJ. Many faces of angioedema: focus on the diagnosis and management of abdominal manifestations of hereditary angioedema. *Eur J Gastroenterol Hepatol*. 2012;24:353–361.

[23] Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis*. 2014;9:99.

[24] Bygum A, Aygören-Pürsün E, Beusterien K, et al. Burden of illness in hereditary angioedema: a conceptual model. *Acta Derm Venereol*. 2015;95: 706–710.

[25] Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc*. 2010;31: 407–414.

[26] Wilson DA, Bork K, Shea EP, Rentz AM, Blaustein MB, Pullman WE. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:314–320.

[27] Longhurst H, Bygum A. The humanistic, societal, and pharmaco-economic burden of angioedema [published online July 7, 2016]. *Clin Rev Allergy Immunol*. http://dx.doi.org/10.1007/s12016-016-8575-2.

[28] Ohsawa I, Honda D, Nagamachi S, et al. Clinical manifestations, diagnosis, and treatment of hereditary angioedema: survey data from 94 physicians in Japan. *Ann Allergy Asthma Immunol*. 2015;114:492–498.

[29] Magerl M, Doumoulakis G, Kalkounou I, et al. Characterization of prodromal symptoms in a large population of patients with hereditary angio-oedema. *Clin Exp Dermatol*. 2014;39:298–303.