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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.