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

Andrea Zanichelli, MD*; Hilary J. Longhurst, MD†; Marcus Maurer, MD‡; Laurence Bouillet, MD, PhD§; Werner Aberer, MD¶; Vincent Fabien, PhD‖; Irmgard Andresen, MD¶; Teresa Caballero, MD, PhD#; for the IOS Study Group**

1 Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milan, ASST Fatebenefratelli Sacco, Milan, Italy
2 Department of Immunology, Barts Health NHS Trust, London, United Kingdom
3 Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité—Universitätsmedizin Berlin, Berlin, Germany
4 National Reference Centre for Angioedema, Internal Medicine Department, Grenoble University Hospital, Grenoble, France
5 Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria
6 Shire, Zug, Switzerland
7 Allergy Department, Hospital La Paz Institute for Health Research, Biomedical Research Network on Rare Diseases (CIBERER, U754), Madrid, Spain

A R T I C L E  I N F O

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A B S T R A C T

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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Reprints: Andrea Zanichelli, MD, Dipartimento di Scienze Biomediche e Cliniche Luigi Sacco, Università degli Studi di Milano-Ospedale Luigi Sacco, Via G.B. Grassi 74, 20157 Milano, Italy; E-mail: andrea.zanichelli@unimi.it.

Disclosures: Dr Zanichelli reported receiving speaker fees from CSL Behring, Shire, Sobi, and ViroPharma (now part of the Shire Group of Companies); receiving consultancy fees from CSL Behring, Shire, and ViroPharma; and acting on the medical/advisory boards for CSL Behring and Shire. Dr Longhurst reported receiving research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, Dyax, Shire/Jerini AG, and ViroPharma. Dr Bouillet reported receiving honoraria from CSL Behring, Pharming, Shire, and ViroPharma, and her institute has received research funding from CSL Behring and Shire. Dr Aberer reported acting as a medical adviser and speaker for CSL Behring and Shire, receiving funding to attend conferences or other educational events, donations to his departmental fund, and participating in clinical trials for Shire. Dr Fabien reported being a full-time employee of Shire, Zug, Switzerland at the time the analysis was conducted and during the development of the manuscript. Dr Andresen reported being a full-time employee of Shire, Zug, Switzerland. Dr Caballero reported receiving speaker fees from CSL Behring, GlaxoSmithKline, MSD, Novartis, and Shire; consultancy fees from CSL Behring, Novartis, Shire, and Sobi; funding for travel and meeting attendance from CSL Behring, Novartis, Pharming, and Shire.

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** Individual collaborators from the IOS Study Group are listed at the end of the article.
**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. 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. 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. Incorrect diagnoses range from allergies to systemic lupus erythematosus, with a variety of treatments, including antihistamines, corticosteroids, and other immunosuppressive therapies, which can have adverse effects and are of limited clinical utility.

Patients with C1-INH-HAE typically experience more than a 10-year delay in diagnosis, 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. The issue of misdiagnosis and its consequences has been previously explored in case studies, post hoc medical record reviews, and country-specific patient registries. 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.

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.

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 used to compare differences between categories, with a statistical significance level of α = 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**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with ≥1 misdiagnoses (n = 185)</th>
<th>Patients without a misdiagnosis (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment, mean (SD) [range], y</td>
<td>43.4 (14.2) [1.0–81.6]</td>
<td>38.5 (15.2) [1.0–81.8]</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td>Female, No. (%) 113 (61.1) 130 (55.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asian 5 (2.7) 4 (1.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other 4 (2.2) 6 (2.6)</td>
<td></td>
</tr>
<tr>
<td>C1-INH-HAE diagnosis, No. (%)</td>
<td>Type I 169 (91.4) 218 (93.6)</td>
<td>15 (6.4)</td>
</tr>
<tr>
<td></td>
<td>Type II 16 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Age at symptom onset, mean (SD) [range], y</td>
<td>14.0 (11.2) [0.1–67.0] 12.9 (11.4) [0.3–77.0]</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, mean (SD) [range], y</td>
<td>29.0 (14.7) [3.8–77.3] 20.4 (15.7) [0.7–77.3]</td>
<td></td>
</tr>
<tr>
<td>Time from symptom onset to C1-INH-HAE diagnosis, mean (SD) [median], y</td>
<td>15.0 (13.4) [11.3] 7.0 (13.2) [1.7]</td>
<td></td>
</tr>
<tr>
<td>No. of attacks per year, mean (SD) [median]</td>
<td>18.9 (21.2) [10.7] 18.9 (27.6) [7.2]</td>
<td></td>
</tr>
<tr>
<td>Frequency of attacks per year, No. (%)</td>
<td>&lt;10 attacks per year 82 (48.8) 123 (56.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥10 attacks per year 86 (51.2) 94 (43.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: C1-INH-HAE, hereditary angioedema due to C1 inhibitor deficiency; HAE, hereditary angioedema.

*Data reported for 183 patients with 1 or more misdiagnoses and 220 patients without a misdiagnosis.

*Data reported for 177 patients with 1 or more misdiagnoses and 204 patients without a misdiagnosis.

*Data reported for 183 patients with 1 or more misdiagnoses and 230 patients without a misdiagnosis.

*Data reported for 183 patients with 1 or more misdiagnoses and 220 patients without a misdiagnosis.

*Data reported for 168 patients with 1 or more misdiagnoses and 217 patients without a misdiagnosis.
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 = .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).

Table 2

<table>
<thead>
<tr>
<th>Patient Misdiagnosis by Family History of HAE</th>
<th>No. (%) of patients with family history of HAE</th>
<th>No. (%) of patients without family history of HAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>140 (41.7)</td>
<td>38 (65.5)</td>
</tr>
<tr>
<td>No</td>
<td>196 (58.3)</td>
<td>20 (34.5)</td>
</tr>
<tr>
<td>Total</td>
<td>336</td>
<td>58</td>
</tr>
</tbody>
</table>

Abbreviation: HAE, hereditary angioedema.

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Table 3

<table>
<thead>
<tr>
<th>Country</th>
<th>No. (%) of patients with ≥1 misdiagnoses (n = 195)</th>
<th>No. (%) of patients without a misdiagnosis (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>11 (84.6)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Brazil</td>
<td>16 (84.2)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Denmark</td>
<td>15 (88.2)</td>
<td>7 (11.8)</td>
</tr>
<tr>
<td>Greece</td>
<td>12 (63.2)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Italy</td>
<td>28 (46.7)</td>
<td>32 (53.3)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>26 (46.4)</td>
<td>30 (53.6)</td>
</tr>
<tr>
<td>Israel</td>
<td>22 (41.5)</td>
<td>31 (58.5)</td>
</tr>
<tr>
<td>Germany</td>
<td>27 (35.5)</td>
<td>49 (64.5)</td>
</tr>
<tr>
<td>France</td>
<td>6 (28.6)</td>
<td>15 (71.4)</td>
</tr>
<tr>
<td>Spain</td>
<td>22 (28.6)</td>
<td>55 (71.4)</td>
</tr>
<tr>
<td>Sweden</td>
<td>0 (0.0)</td>
<td>2 (100.0)</td>
</tr>
</tbody>
</table>

Abbreviations: C1-INH-HAE, hereditary angioedema due to C1 inhibitor deficiency; IOS, Icatibant Outcome Survey.

Table 4

<table>
<thead>
<tr>
<th>IOS country</th>
<th>Year of birth</th>
<th>No. (%) of patients with ≥1 misdiagnoses (n = 195)</th>
<th>No. (%) of patients without a misdiagnosis (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>1950–1959</td>
<td>2 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Brazil</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Denmark</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Greece</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Italy</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Israel</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Germany</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>France</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Spain</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1950–1959</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
</tr>
</tbody>
</table>

Abbreviation: IOS, Icatibant Outcome Survey.

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 experience in receiving the correct diagnosis.
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. 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. Moreover, angioedema is a widely variable disease with different types and subtypes, including acquired angioedema and idiopathic histaminergic angioedema. 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. 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.

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); 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...
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 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.®-® In a recent study by Bygum et al., 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. 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. Increased awareness of C1-INH-HAE signs, symptoms, and prodrum®-® 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.

Acknowledgments


References


