Angiotensin-converting Enzyme Inhibitor-induced Angioedema and Hereditary Angioedema: A Comparison Study of Attack Severity

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Abstract

Objective There appears to be differences in the clinical presentation of hereditary angioedema (HAE) and angiotensin-converting enzyme inhibitor-induced (ACE-I) angioedema (AE). The aim of this study was to compare the clinical characteristics of these two AE forms.

Methods We conducted a retrospective study of consecutive patients with HAE or ACE-I AE. The attack characteristics experienced by the patients were compared by a logistic regression analysis using generalized estimating equations.

Results A total of 56 patients were included in this study (ACE-I AE, n=25; HAE, n=31). A total of 534 attacks were documented. Severe attacks were more common in the patients who had an acute episode of ACE-I AE than HAE. Swelling of the tongue, lips and larynx were significantly associated with ACE-I AE [OR: 8.70 (95% CI, 1.04-73.70), OR: 20.4 (95% CI, 4.9-84.2) and OR: 7.50 (95% CI, 1.20-48.30), respectively].

Conclusion Swelling of the tongue, lips and larynx are significantly more frequent in drug-induced AE than HAE.

Key words: bradykinin, ACE-I AE, emergency, hereditary angioedema

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Introduction

Similar to hereditary angioedema (HAE), angiotensin-converting enzyme inhibitor-induced (ACE-I) angioedema (AE) is mediated by bradykinin (1, 2). Unlike the diagnosis of drug-induced allergic AE, the diagnosis of ACE-I AE is often overlooked, partly due to the time that elapses before AE onset (3). A long interval (mean: 10 years) between symptom onset and diagnosis is also observed in patients with HAE (4). In both these AE forms, the symptoms recur at irregular intervals despite the constant presence of a causal factor, namely, drug exposure in the former and C1 inhibitor (C1-INH) deficiency in the latter (5). Edema attacks are treated by early administration of icatibant, an inhibitor of the bradykinin B2 receptor, or C1-INH concentrate for ACE-I AE or HAE, respectively (6-9). There are currently no standard treatments approved for ACE-I AE or HAE with normal C1-INH, although several case series have described the efficacy of the off-label use of icatibant and C1-INH concentrate (6, 10).

Several retrospective studies have suggested differences in the clinical presentation of ACE-I AE and HAE. AE associated with ACE-I primarily affect the face and upper airways; there are few reports of abdominal pain (5, 11-14). HAE shows a predominance of painful abdominal and peripheral
attacks, although the face and upper airways may also be affected (15). Furthermore, understanding the differences in the clinical presentation between these two main types of AE is especially important for patients seen in the emergency department. The aim of the present retrospective study was to compare the clinical characteristics and the associated attack severity of these two AE populations.

### Materials and Methods

#### Study population

We conducted a single-center retrospective study of consecutive patients with either ACE-I AE or HAE who visited our Reference Center for kinin-mediated AE between January 2002 and March 2012. The analyzed dataset contains data accumulated during the follow-up. Patients could be referred to the referral center directly from the internal medicine department or after admission to the emergency department. Our report meets the STROBE guidelines for the reporting of observational studies (16). All patients with suspected bradykinin-mediated AE (e.g., non-inflammatory, self-limiting, lasting more than 12 hours, recurrent subcutaneous or submucosal swelling of the face, tongue, throat and extremities with the absence of urticaria and itching) received systematic review.

#### Patient inclusion

The inclusion criteria involved a documented diagnosis of ACE-I AE or HAE (type I, II). Patients were included in the study from their first visit to the center. The AE definitions are given in Table 1 (6, 7, 13, 17-20). Exclusion criteria included documented diagnosis of any other AE type: (1) allergic AE associated with a specific causal factor, (2) AE due to an autoimmune disorder, (3) AE due to acquired C1-INH deficiency, (4) AE induced by non-steroidal anti-inflammatory drugs (NSAIDs) which are not mediated by bradykinin, (5) AE due to angiotensin receptor blocker (ARB), (6) HAE with normal C1-INH, and (7) idiopathic histamine-mediated AE (i.e., responding to antihistamines) or non-histamine-mediated AE (i.e., not responding to anti-histamines) in patients with normal C1-INH levels and functional activity, no family history of AE, and no mutation in the F12 gene.

#### Statistical analysis

The results were expressed as medians (25-75 percentiles) for the quantitative variables or numbers (percentages) for the categorical variables. The patient demographics were compared by the Mann-Whitney U test or chi-square test, respectively. The characteristics of the attacks were analyzed by a logistic regression analysis using generalized estimating equations for the correlated data (several attacks in the same patient). The final multivariate model used stepwise ascending variable selection. All analyses were two-way and a p value of <0.05 was considered to be significant. All statistical analyses were conducted utilizing the statistical package R for Windows (version 2.15.1).

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**Table 1. Definitions.**

| AE form              | Definition used                                                                 |
|----------------------|---------------------------------------------------------------------------------|
| HAE                 | Recurrent attacks unresponsive to corticosteroids and antihistamines, in a patient with a family history of AE |
| Type I C1-INH       | Reduced C1-INH level and functional activity                                   |
| Type II C1-INH      | Normal C1-INH level but reduced functional activity                            |
| With normal C1-INH  | Normal C1-INH level and functional activity, responsive to tranexamic acid, with mutation of gene and/or family history of AE ("HAE unknown" if no mutation of F12 gene) |
| Acquired C1-INH     | Reduced C1-INH and C1q levels with autoantibody directed against C1-INH either present (Type II) or absent (Type I), without family history of AE |
| Drug-induced AE     | AE induced by ACE inhibitor, patient receiving treatment with an ACE inhibitor and had no other obvious causes for angioedema |

HAE: hereditary angioedema, C1-INH: C1 inhibitor, ACE: angiotensin-converting enzyme
Results

Patient demographics

A total of 154 consecutive patients presented with AE without urticaria or itching; 98/154 patients were excluded for the reasons shown in Figure. Fifty-six patients, including 25 ACE-I AE patients and 31 HAE patients were studied (Figure). The cohort studied included 24 (43%) men and no difference was seen between gender and AE type (p=0.26). However, patients with ACE-I AE were significantly older than HAE patients [67 (58-72) vs. 39 (25-56); p<0.001].

A family history of AE was present in 25/31 (81%) types I and II patients. The genetic analysis confirmed the diagnosis of AE in the patients with no previous family history of AE. Twenty-three (92%) patients with ACE-I AE and 18 (58%) HAE patients visited the emergency department for an attack (p=0.03). A total of 31 patients from 22 families with HAE C1-INH were evaluated.

The characteristics of the 25 patients with ACE-I AE are given in Table 2. Five (20%) patients were of African descent. All ACE-I AE patients were studied for their C1-INH levels and functional activity and were found to have normal

Table 2. Characteristics of Patients on ACE.

| Characteristic                        | Patients |
|---------------------------------------|----------|
| Patients, n                           | 25       |
| Drugs, n (%)                          |          |
| ramipril                              | 9 (36)   |
| enalapril                             | 6 (24)   |
| perindopril                           | 6 (24)   |
| lisinopril                            | 2 (8)    |
| captopril                             | 1 (4)    |
| quinapril                             | 1 (4)    |
| Indication, n (%)                     |          |
| Hypertension (HT)                     | 19 (76)  |
| Coronary disease with HT              | 3 (12)   |
| Coronary disease without HT           | 1 (4)    |
| Kidney disease                        | 2 (8)    |
| Median interval (25-75 percentiles)   |          |
| (months)                              |          |
| Treatment start – 1st attack          | 8 (1-13) |
| 1st attack – diagnosis                | 1.6 (0.8-4.5) |
| Median number of attacks/patient before diagnosis (25-75 percentiles) | 2 (1-2) |
| Mechanical airway protection, n (%)   |          |
| Intubation                            | 1 (4)    |
| Tracheotomy                           | 2 (8)    |
| n: number of patients                 |          |
Occurrence, treatment and follow-up of acute attacks

Fifty-six patients experienced 534 edematous attacks. Forty-eight attacks occurred in patients with ACE-I AE while 486 attacks occurred in the HAE group. The distribution of the location of the edema was almost constant in the patients. The attacks were severe in 67% of the cases (359/534) (Table 3). Severe attacks were more common in patients with drug-induced AE than HAE. Laryngeal edema occurred in 44% (21/48) of the acute attacks and in 52% (13/25) of the patients with ACE-I AE (Table 3). Both laryngeal edema and facial swelling were more common in patients with ACE-I AE than HAE (p<0.001 and p<0.001, respectively). Conversely, acute attacks of abdominal pain occurred in HAE patients only.

In a multivariate analysis, the factors associated with an acute attack of ACE-I AE were severity of crisis as shown, a higher frequency of laryngeal edema and swelling of the tongue or lips. Conversely, acute abdominal pain was encountered in HAE patients only.

Laryngeal edema occurred in 44% of the acute attacks and in 52% of the patients with ACE-I AE. This prevalence is towards the higher end of the range (2-59%) documented in previous retrospective studies of patients receiving ACE inhibitor treatment (Table 5) (5, 11, 13, 21, 22). This high prevalence may be explained by the severity of the disease in our patients as evidenced by the multiple locations of ACE-I AE. In our study, there was a selection bias of the most severe patients since the vast majority of patients were recruited while in the emergency department. Three of our patients (12%) required mechanical airway protection. This is also in agreement with the prevalence (0-14%) reported in previous studies. Death has also been previously reported, but mortality is probably underestimated due to missed diagnoses (22). Laryngeal edema occurred in a third of our HAE patients but in only 5% of the attacks. In a study with a median follow-up of 5 years, laryngeal edema was found to be a rare event compared to abdominal pain attacks (ratio, 1:54) in 49.6% (61/123) of the patients who experienced laryngeal edema (23). However, the mortality rate in HAE patients is high as evidenced by a recent study which reported 70/214 (33%) of the patients died from asphyxiation (24). Laryngeal edema prompts visits to the emergency department; thus, patients with ACE-I AE, being more prone to laryngeal attacks, are more likely to visit the emergency department than HAE patients (25). Physicians should therefore not forget to question patients who are on renin-angiotensin system (RAS) inhibitors. This knowledge of the potential involvement of the upper airway system in ACE-I AE attacks may enhance management in the emergency department and prevent death.

Tongue swelling was also experienced by a slightly higher proportion of patients with drug-induced AE in our study than previously reported in earlier retrospective studies [56%...
higher end of the range previously documented in earlier
table 5) (5, 11, 13, 21, 22). Our prevalence is towards the
67% of the acute attacks. The reported prevalence is 25-70%
swelling occurred in 64% of our patients and was present in
from massive tongue swelling due to ACE-I AE (26). Lip
seven autopsies in patients who were found to have died
airway obstruction and death as indicated by the results of
13, 21, 22). This complication is serious as it can lead to
(14/25) vs. the published range of 22-52%] (Table 5) (5, 11,
may explain the non-negligible morbidity and mortality rates
for AE (6-9). Corticosteroids and antihistamines are often
the first line treatment for ACE-I AE. The ineffectiveness of
conventional therapy is a characteristic clue suggestive of
bradykinin-mediated AE.

Limitations

The main limitation of our study is its retrospective na-
ture. A number of attacks may have been overlooked as
only those documented in the patients’ files could be ana-
yzed. Moreover, patient reporting of earlier attacks which
had occurred in the home may have been affected by mem-
ory bias. Furthermore, there are many non-inclusion criteria;
however, we focused on bradykinin AE because it can be
distinguished clinically.

Conclusion

Although ACE-I AE and HAE have the same mediator,
clinical differences exist between these two AE forms. Swel-
lng of the larynx, tongue or lips is significantly more fre-
quent in drug-induced AE than the hereditary form, whereas
attacks of abdominal pain are more common in patients with
HAE. This difference likely explains why patients with
ACE-I AE are treated more frequently in the emergency de-
partment.

Author’s disclosure of potential Conflicts of Interest (COI).
Olivier Fain: Advisory role, Shire and CSL Behring.

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