

Life-threatening angioedema induced by angiotensin-converting enzyme inhibitors: Characteristics and risk factors

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ABSTRACT

Background: Angioedema induced by angiotensin-converting enzyme inhibitors (ACEIs) is a well-known phenomenon and roughly accounts for one-third of angioedema cases presenting to the emergency departments. This study aimed to characterize the patients with severe reactions that required hospitalization and tried to identify the risk factors for these life-threatening events.

Methods: The records of all patients hospitalized with the diagnosis of "angioedema" over a 10-year period were retrospectively analyzed. Patients' characteristics as well as the characteristics of the angioedema-induced hospitalizations were studied.

Results: In 46 of 165 patients (28%) the angioedema was ACEI induced. The severity of the event was mild in 12 patients (26%), moderate in 25 patients (54%), and severe in 9 patients (19%). Twelve patients (26%) were admitted to the intensive care unit and six patients (13%) underwent intubation. Epinephrine was administered to 13 patients (29%), steroids were administered to 40 patients (87%), and anti-histamines were administered to 36 patients (78%). One patient died as a consequence of the event (2%). Twenty patients (45%), including the deceased patient, had recurrent events of angioedema before admission. Obese patients had significantly more recurrent events compared with nonobese patients ($p = 0.03$). There was also a tendency for more severe events in the obese patients ($p = 0.079$). Diabetes was significantly associated with moderate-to-severe events ($p = 0.009$) whereas treatment with beta-blockers or diuretics was significantly associated with milder events ($p = 0.007$ and $p = 0.044$, respectively).

Conclusion: The high recurrence rate of ACEI-induced angioedema preceding subsequent life-threatening events suggests underdiagnosis of this potentially fatal adverse reaction. Diabetes and probably obesity are risk factors for more severe events. Physicians following patients receiving ACEI should be more aware of possible shortcomings associated with these medications.

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Angiotensin-converting enzyme inhibitors (ACEIs) are of the most frequently prescribed medications in the Western world, given as first-line treatment to millions of patients suffering from hypertension, congestive heart failure (CHF), and diabetic nephropathy. As a class of drugs, ACEIs are generally well tolerated with the most common side effects being hypotension, hyperkalemia, dry cough, dizziness, rise of blood urea nitrogen and creatinine, and fatigue.¹ Another less common adverse effect of this class of drugs is angioedema, with an estimated frequency of 0.1–2.2% among users.² Although relatively rare, because of the high prescription rate of these medications the actual incidence of patients suffering from ACEI-induced angioedema is considerable and hospitalizations due to this adverse drug event keep rising; in a rough estimation in ~30–45% of the patients turning to emergency departments due to angioedema, the cause is use of ACEI.^{3–7} Often, the angioedema appears in the face (swelling of the lips, cheeks, or eye lids) and sometimes goes unnoticed and resolves spontaneously within a few hours to a few days. In some of the events, this phenomenon might become more serious when involving the gastrointestinal tract, causing bowel obstruction, or when involving the upper airways, causing narrowing and blockade of the upper airway. Obstruction of the upper airway calls for an immediate intubation and airway protection and if delayed it may be fatal.^{8,9} The exact reason why ACEI-related angioedema appears only in certain patients and in certain timing is unknown.

There are only few known risk factors to this adverse effect: among the American population the incidence of angioedema due to ACEI treatment in black patients is twice as high as in nonblack patients. Similarly, the incidence is almost double in patients with heart failure

compared with patients with normal heart function.^{2,10} Surprisingly, in patients with diabetes there is lower risk of developing ACEI-related angioedema.² Other suggested risk factors are female gender, C1 inhibitor deficiency, concomitant treatment with statins and sirolimus, smoking, seasonal allergies, nonsteroidal anti-inflammatory drug use, age >65 years, a history of ACEI-induced cough,³ and alcohol-related diseases.¹¹ Suggested risk factors for life-threatening angioedema are obesity and a history of previous manipulation or trauma of the upper airways resulting in permanent narrowing of the airways.^{12,13}

In the present study we concentrated on the more severe ACEI-induced angioedema events, which required hospitalization. Our aim was to characterize these patients in comparison with non-ACEI-induced angioedema patients and to identify the risk factors for life-threatening events among the local Israeli population.

METHODS

Study Population and Data Extraction

All patients admitted to Meir Hospital during the years 2003–2012 that were given a diagnosis of angioedema were eligible for this study. A retrospective analysis of their computed records was performed. The study was approved by the local ethics committee.

For each patient the following data were extracted: age and gender and medical information including obesity (body mass index, >30), malignancy, diabetes, and laboratory values of hemoglobin and C1 inhibitor or C4. Concomitant drug treatment was extracted as well and included the following medications: anticoagulants, Eltroxin (Aspen, Perrigo, Israel), omeprazole, aspirin, ACEI, β -blockers, angiotensin receptor blockers, α -blockers, other vasodilators (nitrates and pentoxifyllin), calcium channel blockers, diuretics, diabetes control agents, and statins. Information about additional comorbidities included CHF, ischemic heart disease (IHD), cardiovascular accident (CVA), past or present heavy smoking, and renal failure represented by elevated serum creatinine level. These data were extracted later only for patients diagnosed with ACEI-induced angioedema.

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Description of the Reaction

Data regarding the event of angioedema leading to hospitalization was sorted according to the anatomic presentation and severity. Anatomic presentation included localization of angioedema to head and neck, other parts of the body, or generalized and whether or not it was accompanied by a rash. The severity of the reaction was graded as mild, moderate, or severe: "mild", if angioedema involved only a small limited skin areas or angioedema of the lips; "moderate" reaction included angioedema of the tongue or neck without difficulty of breathing or when involving the gastrointestinal tract; "severe" reaction included objective respiratory distress, hemodynamic, or neurological compromise.

ACEI-Induced Angioedema

Angioedema was considered ACEI induced when the patient was treated with the drug and there was no other possible cause for angioedema as evaluated by the admitting physician and the allergist reviewing the record. ACEI was not suspected as the cause if angioedema recurred after more than a month since cessation of ACEI treatment¹⁴ or if there was an accompanying urticaria; we included as ACEI-related angioedema events with a minimal rash/redness other than urticaria.

Other causes of angioedema included other known drug or food allergy, accompanying infection or inflammatory state, hereditary angioedema, angioedema of unknown cause (including chronic urticaria and angioedema), and angioedema accompanying a thrombotic event—a new entity we suggest and will be discussed later.

Statistical Analysis

Data were described as numbers and percentage for nominal parameters and as mean $\pm$ SD—for continuous variables. Chi-square was used to find differences between categorical variable or Fisher's exact test—each when appropriate. The value of $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS-19 software (SPSS, Inc., Chicago, IL).

RESULTS

Demographics

To give a notion of the size of population Meir Hospital serves, there are, on average, 150,000 emergency department visits in a year and an average of 66,000 admissions a year. During the years 2003–2012, 673,665 patients were admitted to the hospital. Of them 202 patients were hospitalized due to angioedema.

One hundred two were male and 100 female patients. Their age was 46.5 ± 23 years (mean $\pm$ SD). From this group we excluded 37 patients either because of lack of information (19 patients), wrong diagnosis (*e.g.*, localized swelling due to infection, chronic swelling secondary to skin disease, *etc.*),¹⁰ or patients in whom the diagnosis of "angioedema" was related to past episode rather than the current admission.⁸ Our study population was comprised of the remaining 165 patients. Their mean age was 52 ± 24 years (mean $\pm$ SD; male/female, 52:48%). There were 17 patients <18 years old.

Causes of Angioedema Leading to Admissions

In 46 patients (28% of the study population and 31% of the adult population) the angioedema was induced by ACEI treatment. Other causes of angioedema requiring hospitalization were idiopathic (34%; $n = 56$), hereditary angioedema (0.6%; $n = 1$), infectious or inflammatory illness (5.5%; $n = 9$), another drug (23%; $n = 38$), insect sting/snake bite (4%; $n = 6$), and food allergy (4%; $n = 6$). Through our research we identified three patients who presented with angioedema as the first clinical sign of a major thromboembolic event (pulmonary embolism, deep vein thrombosis, and/or CVA) in a site

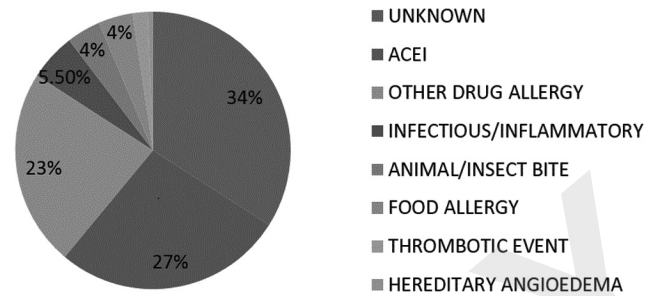


Figure 1. Causes of angioedema leading to hospitalization.

remote from the site of thrombosis. This entity is proposed as a rare cause of acute angioedema and it is further elaborated in the Discussion section (Fig. 1).

C1 Esterase Inhibitor Deficiency

In most of the patients (107/165) C4 or C1 esterase values were not measured. When measured, in 58 patients, C4 was within normal values among all patients.

There was a single patient with a known diagnosis of hereditary angioedema, and his complement levels were not measured throughout his admission;

Characteristics of Patients with ACEI-Induced Angioedema

In 46 patients angioedema events were induced by to ACEI treatment. In comparison with patients with non-ACEI-induced angioedema, patients with ACEI-induced angioedema were significantly older (mean age, 74 and 43 years, respectively; $p = 0.000$) and there was a higher rate of male patients (63 and 48%, respectively; $p = 0.08$; Table 1).

When compared with non-ACEI-induced angioedema, patients with ACEI-induced angioedema were receiving significantly more other concomitant drugs: 34/46 patients (86%) received two or more additional drugs, compared with 32/119 (27%) with the non-ACEI-induced angioedema ($p < 0.0001$). Patients with ACEI-induced angioedema had lower hemoglobin levels (mean Hb, 12.8 ± 1.5 versus 13.4 ± 1.7 ; $p = 0.028$), and a diagnosis of malignancy was more prevalent among them (19% compared with 10%; $p = 0.025$). Patients with ACEI-induced angioedema showed a tendency for higher rate of obesity (52% versus 45%; $p = 0.28$). It should be noted that information about weight or diagnosis of obesity was available for only 40% of the patients with the ACEI-induced angioedema and for 64% of the non-ACEI-induced patients.

Description of the Reaction

Angioedema induced by ACEI was accompanied by rash in 4 patients (8.7%) whereas angioedema due to other causes was accompanied by rash in almost one-half of the cases (55 patients; 46%; $p = 0.000$). Angioedema involving head and neck was found in 95% of the events leading to hospitalization both in the ACEI-induced patients and the non-ACEI-induced patients. Involvement of other body parts (usually limbs) occurred less often in the ACEI-induced group (10% versus 23%; $p = 0.068$).

Severity Grading of ACEI-Induced Angioedema Events

In 12 patients (26%) the severity of the event was graded as mild, in 25 patients (54%) as moderate, and in 9 patients (19%) as severe. Twelve patients (26%) were admitted to the intensive care unit and six patients (13%) underwent intubation. Treatment with epinephrine

Table 1 Patients' characteristics

	ACEI-Induced Angioedema (n; %)	Angioedema not Induced by ACEI (n; %)	<i>p</i> Value
Patients	46	119	
Age (mean $\pm$ SD), yr	74 $\pm$ 12	44 $\pm$ 23	0.000*
Male	29 (63%)	57 (48%)	0.081
Comorbidity			
Obesity	9 of 17 (52%)	37 of 81 (45%)	0.280
Hemoglobin (mean $\pm$ SD)	12.8 $\pm$ 1.5	13.5 $\pm$ 1.7	0.028*
Malignancy	9 (19%)	13 (10%)	0.025*
Creatinine (mean $\pm$ SD)	1.3 $\pm$ 0.4	Data not obtained	
Heavy smoking	14 (30%)	Data not obtained	
CHF	11 (24%)	Data not obtained	
CVA	10 (21%)	Data not obtained	
IHD	18 (39%)	Data not obtained	
Concomitant drug treatment			
ACEI	46 (100%)	12 (10%)	0.000*
Anticoagulant	6 (13%)	3 (2%)	0.006*
Omeprazole	9 (19%)	9 (7%)	0.028*
Aspirin	29 (63%)	22 (18%)	0.000*
β -Blockers	16 (34%)	12 (10%)	0.000*
α -Blockers	7 (15%)	4 (3%)	0.007*
Vasodilators	5 (10%)	5 (4%)	0.111
Calcium channel blockers	18 (39%)	10 (8%)	0.000*
Diuretics	22 (47%)	12 (10%)	0.000*
Anti-glycemic agents	14 (30%)	18 (15%)	0.026*
Statin	27 (58%)	23 (19%)	0.000*
Eltroxin	2 (4%)	8 (6%)	0.551
Angiotensin receptor blocker	1 (2%)	5 (4%)	0.527
Severity grading of angioedema event			
Mild	12 (26%)	47 (39%)	0.251
Moderate	25 (54%)	49 (41%)	0.251
Severe	9 (20%)	23 (20%)	0.251
Intubation	6 (13%)	5 (4%)	0.041*
Admission to ICU	12 (26%)	22 (19%)	0.291
Adrenaline treatment	13 (29%)	45 (38%)	0.286

**p* < 0.005.

ACEIs = angiotensin-converting enzyme inhibitors; CHF = congestive heart failure; CVA = cerebrovascular accident; IHD = ischemic heart disease; ICU = intensive care unit.

was given to 29% of the patients (13 patients), steroids were given to 40 of the patients (87%), and antihistamines were given to 36 of the patients (78%). One patient died as a consequence of the event (2%). Twenty patients (45%), including the deceased patient, had recurrent events of angioedema before admission.

In comparison with non-ACEI-related events (angioedema due to other causes) we found no significant difference in the graded severity (20% severe), rate of intubations (4%), admission to the intensive care unit (18%), or use of epinephrine (38%).

Risk factors for a Moderate-to-Severe ACEI-Induced Angioedema Event

Age or gender were not associated with the degree of severity of the events.

Comorbidities, including heavy smoking, IHD, CHF, CVA, renal failure (represented by creatinine level), and anemia (represented by hemoglobin level), were not significantly associated with the severity of the events, although patients with CHF, IHD, and CVA showed a trend toward a milder event. Thus, 5 of 11 patients with CHF (45%) had a mild event compared with 6 of 34 patients without CHF (18%; *p* = 0.062). Seven of 18 patients with IHD (39%) had a mild event compared with 4 of 27 patients without IHD (15%; *p* = 0.066), and 4

of 10 patients with CVA (40%) had a mild event compared with 7 of 35 patients without CVA (20%; *p* = 0.194).

Obesity. As previously mentioned, information about weight or diagnosis of obesity was available in only 40% of the patients with ACEI-induced angioedema (17 patients). Obese patients had significantly more recurrent events compared with nonobese patients (7 of 9 patients [78%] versus 2 of 8 nonobese patients [25%]; *p* = 0.03). Obesity was associated with the more severe events: moderate or severe events occurred in 8 of 9 of the obese patients (89%) compared with 4 of 8 (50%) of the nonobese patients (*p* = 0.079). There was a tendency for more frequent intubation in obese patients (3 of 9 [33%] versus 1 of 8 [12%]; *p* = 0.3).

Concomitant Drug Treatment and Severity of Events

Consumption of antidiabetic medications (metformin, sulfonylurea, insulin, and rosiglitazone) was significantly associated with moderate and severe events (14 of 14 patients [100%] versus 20 of 32 in patients not receiving these medication; *p* = 0.009; Table 2). It is important to point out that none of these patients was treated with oral hypoglycemic agents of the dipeptidyl peptidase family that are known to contribute to the phenomenon of ACEI-induced angioedema by raising bradykinin levels.¹⁵

Table 2 ACEI-induced angioedema—possible risk factors for a more severe reaction

	Patients with Mild Angioedema (n; %)	Patients with Moderate–Severe Angioedema (n; %)	<i>p</i> Value
Patients	12 (26%)	34 (74%)	
Age (mean ± SD), yr	74.2 ± 12	72.9 ± 11	0.775
Male	8 (67%)	21 (62%)	0.762
Female	4 (33%)	13 (38%)	
Comorbidity: <i>p</i> value in comparison with patients without the specific comorbidity			
Obesity	2 (33%)	9 (69%)	0.141
Hemoglobin (mean ± SD)	12.6 ± 1.6	12.9 ± 1.4	0.463
Creatinine (mean ± SD)	1.3 ± 0.4	1.1 ± 0.3	0.163
CHF	5 (41%)	6 (17%)	0.062
Malignancy	2 (16%)	7 (20%)	0.768
IHD	7 (58%)	11 (32%)	0.066
CVA	4 (33%)	6 (17%)	0.194
Heavy smoking	4 (33%)	10 (29%)	0.089
Concomitant drug treatment: <i>p</i> value in comparison with patients without the specific drug tx			
Anticoagulant	3 (25%)	3 (8%)	0.128
Omeprazole	3 (25%)	6 (17%)	0.581
Aspirin	8 (67%)	21 (61%)	0.762
β-Blockers	8 (67%)	8 (23%)	0.007*
α-Blockers	1 (8%)	6 (17%)	0.440
Vasodilators	3 (25%)	2 (5%)	0.067
Calcium channel blockers	4 (33%)	14 (41%)	0.632
Diuretics	9 (75%)	13 (38%)	0.044*
Antidiabetic agents	0 (0%)	14 (41%)	0.009*
Statin	8 (67%)	19 (55%)	0.514

**p* < 0.05.

ACEI = angiotensin converting enzyme inhibitors; CHF = congestive heart failure; CVA = cerebrovascular accident; IHD = ischemic heart disease.

Treatment with β-blockers or diuretics was significantly associated with a milder event: mild reaction was observed in 8 of 16 (50%) patients treated with β-blockers compared with 4 of 30 (13%) patients not treated with them (*p* = 0.007). Mild reaction was observed in 9 of 22 (40%) patients treated with diuretics compared with 3 of 24 (12%) patients not treated with diuretics (*p* = 0.044). We found no other significant association between other concomitant medications and the severity of the event.

DISCUSSION

ACEI-induced angioedema is an infrequent but well-described adverse event of this group of medications. Although rather rare, it conveys a lethal potential. In the current study we aimed to characterize this phenomenon compared with other causes of angioedema and to identify possible risk factors for the occurrence of severe life-threatening events. We found that in 31% of the adult patients hospitalized because of angioedema, it could be attributed to the usage of ACEI. Not surprisingly, we found that these patients were significantly older than patients with angioedema related to other causes. This can be attributed to the more common usage of ACEI in this age group. Similarly, older age can also explain the significant difference in comorbidities (multidrug treatment, anemia, and malignancy).

The strength of our study is its focus on patients with severe ACEI-induced angioedema that required hospitalization for further observation or treatment, in contrary to other studies that described all patients with ACEI-induced angioedema evaluated and treated in the emergency departments, disregarding the severity of the event.^{5,6}

Our main goal was to identify possible risk factors for a severe reaction leading to hospitalization. Several factors were evaluated.

Gender

In contrast to previous reports that speculated that female patients were more prone to develop ACEI-induced angioedema (3) there were more males (63%) in our population who were admitted with ACEI-induced angioedema, although gender was not associated with the grade of severity of the events.

Age and Comorbidities

It could be expected that older age and comorbidities would be associated with more severe events. Nevertheless, this was not the case and patients with CHF, IHD, and CVA even showed a trend to develop milder events. This association may be the result of a reversed causality—an inclination to hospitalize older and sicker patients, even with a mild angioedema event.

Obesity

Information about patients' weight was available on only 40% of the patients with ACEI-induced angioedema; paucity of information regarding this important factor makes it impossible to draw conclusions of the association between obesity and ACEI-induced angioedema; however, under consideration of this limitation, it is worth mentioning that in our study obesity was a risk factor for recurrent events of angioedema before admission, and we also detected a trend toward a more severe reaction among obese patients.

In light of these findings and of previous reports suggesting obesity as a risk factor for life-threatening angioedema, we strongly suggest questioning this association in future larger-scale studies.

Concomitant Drug Treatment

Patients diagnosed and treated for diabetes had significantly more severe events. This is in contrary to previous reports about the association of diabetes and ACEI-induced angioedema.² We also found that administration of β -blockers or diuretics was significantly associated with a milder event.

We can not explain these associations or tell whether these drugs directly protect from severe angioedema events. Possibly, it was merely another reflection of the previously mentioned reversed causality between hospitalizations of sicker patients with milder events. A multivariate logistic regression model comprising all of the different parameters attempting to define the relative contribution of each risk factor (age, gender, specific drugs, and comorbidities) was not informative because of the relatively small size of the group compared with its heterogeneity.

A recently published retrospective study, describing 100 patients presenting to the emergency department with ACEI-induced angioedema, also addressed the question of the effect of concomitant medications taken: 66% of the patients were admitted. Concomitant medications did not differ between patients who were admitted and those who were discharged home.¹¹

Angioedema Accompanying a Thromboembolic Event

In the current study three patients presented with angioedema followed by a thromboembolic event. This observation adds to previous reports showing an interplay between an inflammation and coagulation as a pathomechanism in urticaria and angioedema.^{16,17} Accordingly, thromboembolism should be considered as a possible association of acute angioedema; further studies will be necessary to verify and extend this observation.

Because ACEIs are used worldwide by millions of patients, and because ACEI-induced angioedema is one of the less prevalent side effects of these drugs, studies aiming to identify risk factors for ACEI-induced angioedema should be conducted as prospective cohort studies with large study populations in a scale of at least several thousands of patients. Our study was conducted as a retrospective single-center study and therefore bears the weakness of a small-scale study. However, our unique view point enabled us to focus on analyzing the more serious and severe events, and, as such, the size of our study population is worthy.

In a patient treated with ACEI and presenting with angioedema, the diagnosis of ACEI-induced angioedema is a diagnosis made by exclusion of other possible causes.¹⁸ Hence, it is more than possible that in our study there is an "innate" bias toward overdiagnosis of this phenomenon. However, the retrospective nature of our study enabled us to follow the medical history of the patients and to minimize this bias.

One of the striking findings of our study was that although 45% of the hospitalized patients with ACEI-related angioedema had previous events of angioedema, administration of ACEI was not discontinued by their primary physicians. This may be caused either by patients' underreporting of these events or by failure of the physicians to act properly once angioedema is reported by a patient receiving ACEI. Both patients taking ACEI as well as physicians prescribing them should be better aware of the potential morbidity and even mortality associated with these commonly used medications. This high incidence of previous events of angioedema that did not result in discontinuation of the drugs suggests underdiagnosis of this

potential severe adverse reaction of ACEI by the primary physician in the community. Raising the awareness of primary physicians to this phenomenon and encouraging them to actively inquire patients about it may decrease morbidity and mortality associated with ACEI-induced angioedema.

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