



Profile of Serious Angioedema Requiring an Urgent Advice from a National Reference Call Center

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Abstract

Introduction: Angioedema (AE) is a reason for emergency care when it is severe. Care is difficult when the diagnostic is not known before the attack: Mast Cell (MC) or Bradykinin (BK) mediated. One is very common but often benign, the other rare but potentially fatal. The French national reference center of AE (CREAK) provides emergency physicians with a hotline and a guideline to help them manage their patients.

Objective: This study aimed to describe the clinical features of AE episodes prompting a call on the CREAK hotline and classify patients depending on the suspected cause of the AE.

Methods: It's a retrospective study between March and August 2018. Each physician calling on the CREAK hotline was asked to fill a clinical description form for the AE emergency. Known patients of CREAK were excluded.

Results: A 84 patients were included. 41 (48.8%) in the angiotensin converting enzyme inhibitors induced AE (ACEi-AAE), 39 (46.4%) in the MC-AE, and 4 (4.8%) in the BK-AE. The MC-AE patients have more history of hives than ACEi-AAE: 29%, 3% vs. 2%, 4%, p=0.0004. The ACEi-AAE patients are older: 69 (28-58) years vs. 40, 5 (62-75) years, p<0.00001. ACEi-AAE mainly affected the tongue and ENT: 58%, 5% vs. 25%, 6%, p=0.003 and 29%, 3% vs. 13%, p=0.001. ACEi-AAE is more transferred to intensive care units.

Conclusion: All the doctors who called the hotline appreciate this tele-expertise especially in case of ACEi-AAE presumptions. In addition to providing rapid AE expertise, this service also allows to educate physicians in the management of AE irrespective of its origin.

Keywords: Angioedema; Emergency department; Hotline; ACEi; Tele-expertise

Introduction

Angioedema is defined by a sudden, localized swelling of the mucous membranes and the deep layers of the skin that regress over hours or days. It's caused by vascular leakage induced by vasoactive substances. It can affect any part of the body, but often affects the eyelids, lips, hands, feet, genitals and the respiratory and digestive tracts. It may be associated with hives. Angioedema accounts for 80,000 to 112,000 Emergency Department (ED) visits per year in USA [1]. Data from Italy suggest that 0.37% of all ED visits are related to angioedema and Canadian study estimated that 1:1000 ED visits are angioedema related [2,3].

Isolated AE are classified depending on their causal vasoactive mediator (Figure 1). Thus, two broad categories of AE are identified: Mast cell induced AE (MC-AE) caused mostly by histamine and Bradykinin mediated AE (BK-AE) [4]. MC-AE is mainly spontaneous and looks like spontaneous urticaria. Sometimes, they are associated with NSAID. Isolated AE are rarely the symptoms of anaphylaxis. Allergic AEs are often associated with digestive and respiratory signs, diffuse erythema and shock. BK-AE can be associated with C1 INH deficiency (hereditary or acquired) but the most frequent are Angiotensin Converting Enzyme Inhibitors (ACEi) induced AE. It affects 0.7% of ACEi users. In France, we have estimated that it represents 5000 patients a year [5,6].

In ED, patients referred for a serious AE (face or respiratory tract) are a diagnosis and therapeutic challenge. BK-AE may be lethal, and require specific, onerous treatments, with limited availability, while MC-AE (with the exception of anaphylaxis) is exceptionally fatal and very common. Thus, BK-AE has a 45-fold higher mortality risk than MC-AE [7]. Often patient can't speak because of the

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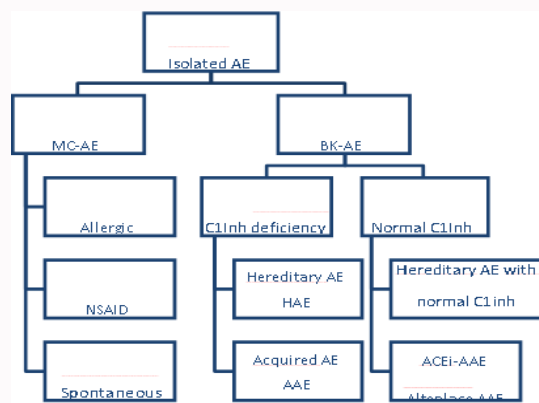


Figure 1: Etiologies of angioedema.

NSAID: Non Steroid Anti-Inflammatory Drugs; MC-AE: Mast Cell induced Angioedema; BK-AE: Bradykinin Mediated Angioedema; C1Inh: C1Inhibitor; ACEi: Angiotensin Converting Enzyme Inhibitors

ENT localization of angioedema. It's impossible to conduct a detailed interrogation. Physicians must treat quickly the patient without waiting for the results of laboratory tests.

In 2011, French National Reference Center for Angioedema (CREAK) created national tele- assistance for known patients with HAE. Then, in a second step, this hotline was available for all French emergency doctors to help them with diagnostic and therapeutic management of AE. This call center is available 24 h a day and concerns all types of angioedema. The CREAK created and distributed a guideline for the management of AE in emergencies with the phone number (posters in doctors' offices) (Figure 2) [8]. This study aimed to describe the clinical features of AE episodes prompting a call on the national AE hotline.

Materials and Methods

We have done a retrospective study from 1st March to 31st July 2018. Every physician that called the national CREAK hotline was asked to fill a form with clinical data concerning the AE episode prompting the call. The collected data was the age, sex, personal or familial history of AE or urticaria, the location of the AE, the duration of the episode, and treatments administered before the call. In case of missing information, patients were directly contacted if they had given their consent to a follow up call. Calls concerning known patients of the CREAK were excluded.

Quantitative variables were expressed as means and standard deviations if normally distributed (as determined by Shapiro-Wilk), otherwise they were expressed as median and range (25th to 75th percentile). Qualitative variables were expressed as percentages.

Quantitative variables were compared by Kruskal Wallis or Students T test. Qualitative variables were compared by Fisher's exact test or Chi-square test. Results were considered statistically significant for a p-value inferior to 0.05.

Results

The 135 calls were made during the study. The 33 concerned known patients of the CREAK. The 2 calls concerned the same patient, and the second call was not included. The 17 calls were excluded due to lacking clinical information.

The characteristics of the study population are summarized in Table 1. The duration of the AE episode was under 24 h in 48 patients

(57.1%), from 24 h to 72 h in 21 patients (25%) and over 72 h for 9 patients (10.7%). 83 patients had AE, 17 had AE associated with hives, and one patient had isolated hives.

AE affected the face in 55 patients (65.5%), the tongue in 36 patients (42.9%), ENT in 19 patients (22.6%), extremities in 7 patients (8.3%), and 3 patients complained of abdominal pain (3.6%) (Table 1). The 29 patients had several simultaneous locations of AE (34.5%). The 80 patients received antihistamines (95.2%), 44 steroids (52.4%), 15 adrenalin (17.9%, 13 by inhalation, 2 intravenously), 17 received Icatibant (20.2%), 5 received human C1 inhibitor (6%). The 9 patients were transferred to an intensive care unit, 2 of which were intubated. The diagnostic assumptions were 49% of ACEi-AAE, 46.3% of MC-AE and 4.7% of BK-AE.

BK-AE

A BK-AE is suspicious in 4 patients (4.7%), 3 female and one male. The median age in this group was 28 years (8-53.5). The 2 had prior history of AE (50%), none had prior history of hives. No patients were treated by ACEi or ARB. None reported familial history of AE.

The duration of the AE episode between 24 h and 72 h in 2 patients (50%) and over 72 h in 2 patients (50%). The 4 patients had no hives. The AE was located at the face in 2 patients (50%), ENT in 2 patients (50%). The 2 patients (50%) had several simultaneous locations of AE. Administered treatments at the time of call were antihistamines for 4 patients (100%), steroids for 1 patient (25%), intravenous adrenaline for 1 patient (25%), and 3 patients received Icatibant or C1 inhibitor. One patient was intubated in the ICU.

ACEi-AAE

An ACEi-AAE is suspicious in 41 patients (Table 1). The median age in this group was 69 years (62 years to 75 years). The 22 had had at least one episode of AE prior to the call (53.7%). The duration of the AE episode was less than 24 h in 24 patients (58.5%), between 24 h and 72 h in 12 patients (29.3%) and over 72 h in only 3 patients (7.3%).

The AE was located at the tongue in 24 patients (58.5% of the ACEi-AAE), the face in 22 patients (53.7%), the ENT in 19 patients (29.3%), the extremities in one patient (2.4%), and one patient had abdominal pain associated with AE of the face (2.4%). 15 patients (36.6%) had several simultaneous locations of AE.

Administered treatments at the time of call were antihistamines

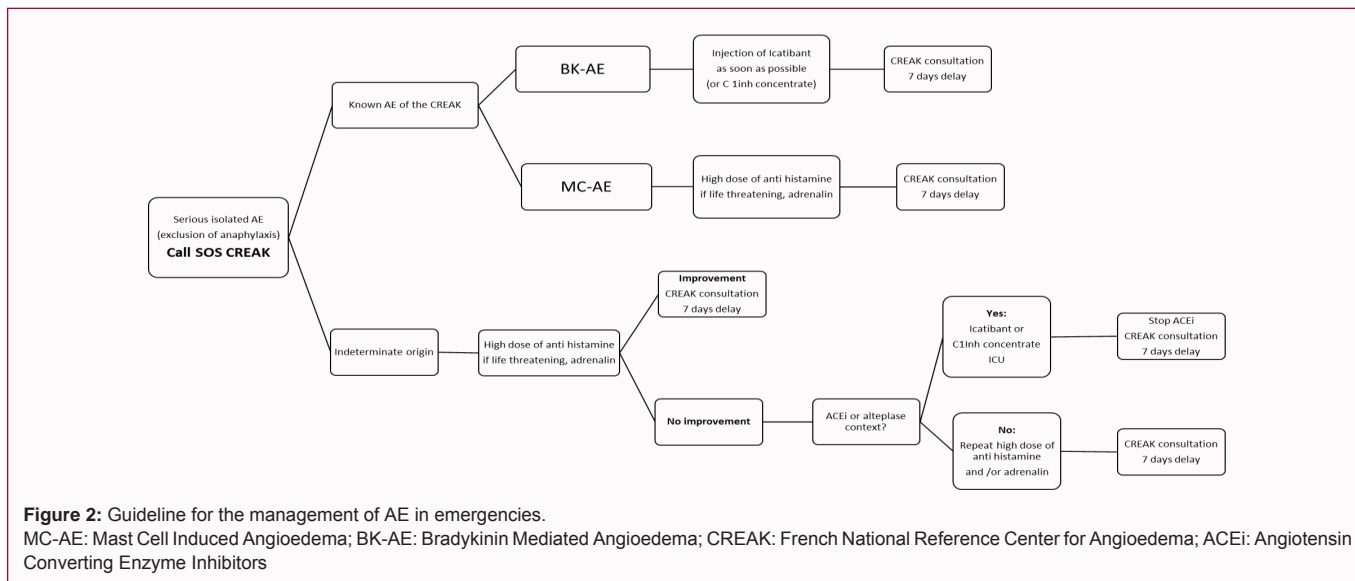


Figure 2: Guideline for the management of AE in emergencies.

MC-AE: Mast Cell Induced Angioedema; BK-AE: Bradykinin Mediated Angioedema; CREAK: French National Reference Center for Angioedema; ACEi: Angiotensin Converting Enzyme Inhibitors

Table 1: Description of the Angioedema (AE) attacks.

	Total	MC-AE Presumption	ACEi-AE Presumption	p
N (%)	84	39 (46.4%)	41 (49%)	na
Sex ratio F/H	1	1.1	0.7	0.37
Age (median) years	59 (39-69.5)	40.5 (28-58)	69 (62-75)	< 0.00001
History of	45 (53.6%)	21 (54%)	22 (53.7%)	0.92
AE	13 (15.5%)	12 (29.3%)	1 (2.4%)	0.0004
Hives				
ACEi	45 (51%)	4 (10.3%)	41 (100%)	na
Episode Duration	48 (57%)	24 (61.5%)	24 (58.5%)	0.64
< 24h	21 (25%)	7 (18%)	12 (29.3%)	0.26
24 h to 72 h	9 (10.7%)	5 (13%)	3 (7.3%)	0.47
>72 h				
AE location	55 (65.5%)	31 (79.5%)	22 (53.7%)	0.015
Face	36 (43%)	10 (25.6%)	24 (58.5%)	0.003
Tongue	19 (22.6%)	5 (13%)	19 (29.3%)	0.001
ENT	7 (8.3%)	6 (15.4%)	1 (2.4%)	0.054
Extremities	29 (34.5%)	12 (31%)	15 (36.6%)	0.58
Multiple locations				
Abdominal pain	3 (3.6%)	2 (5%)	1 (2.4%)	0.61
Concomitant hives	3 (3.6%)	17 (43.6%)	0	Na
Treatments	80 (95%)	39 (100%)	37 (90%)	0.11
Anti histamine	44 (52.4%)	19 (48.7%)	24 (58.5%)	0.38
Steroids	15 (18%)	6 (15.4%)	8 (19.5%)	0.63
Adrenalin	22 (26%)	0	19 (46.3%)	Na
Icatibant/C1 INH				
ICU Transfer	9 (10.7%)	1 (2.6%)	7 (17%)	0.057

MC-AE: Mast Cell Induced Angioedema; Acei-AE: Angiotensin Converting Enzyme Inhibitors Induced Angioedema; ICU: Intensive Care Unit

for 37 patients (90.2%), steroids for 24 patients (58.5%), adrenaline for 8 patients (19.5%, 7 by inhalation, 1 intravenously), and Icatibant or human C1 inhibitor for 19 patients (46.4%). 7 patients (17.1%) were transferred to an intensive care unit. It is interesting to note that 3 patients were treated also by mTOR inhibitors, 3 by Dipeptidyl peptidase 4 inhibitors.

MC-AE

A MC-AE is suspicious in 39 patients (Table 1). The median age in this group was 40.5 years (28 years to 57.8 years). The 21 had prior history of AE (53.9% of the MC-AE group) 12 patients (29.3%) had prior history of hives. The 4 patients were treated by ACEi (but were classified in this group due to the presence of hives during the AE

episode). The duration of the AE episode was less than 24 h in 24 patients (61.5%), between 24 h and 72 h in 7 patients (18%) and over 72 h in 5 patients (12.8%).

During the episode prompting the call, 17 had AE and hives (43.6%), only one patient having only hives. The AE was located at the face in 31 patients (79.5%), tongue in 10 patients (25.6%), extremities in 6 patients (15.4%), ENT in 5 patients (12.8%) and 2 patients had abdominal pain during the episode (5.1%). The 12 patients (30.8%) had several simultaneous locations of AE.

Administered treatments at the time of call were antihistamines for 39 patients (100%), steroids for 19 patients (58.5%), inhaled adrenaline for 6 patients (15.4%). One patient was transferred to an ICU without intubation. No patients were treated by Icatibant or C1 inhibitor.

Comparison between ACEi-AAE and MC-AE

The MC-AE patients have more history of hives than ACEi-AAE: 29%, 3% vs. 2%, 4%, $p=0.0004$. The ACEi-AAE patients are older: 69 (28-58) years vs. 40, 5 (62-75) years, $p<0.00001$. ACEi-AAE mainly affected the tongue and ENT: 58%, 5% vs. 25%, 6%, $p=0.003$ and 29, 3% vs. 13%, $p=0.001$. ACEi-AAE is more transferred to intensive care units: 17% vs. 2.6, $p=0.057$.

Caller origin

The 56 calls were made from an ED (66.6%), 11 from an Intensive care unit (13.1%), 7 from an inpatient facility (8.3%: 4 from internal medicine wards, 1 from a hematology, dermatology and pediatric ward), 6 from outpatient family physicians' practices, 4 from an unknown location (Figure 2). The 48 calls were made from a general hospital (57.1%), 26 from a teaching hospital (30.9%), and 6 from private practice offices.

Discussion

In an Italian tertiary center, Zingale et al. [9] reported that 49% of isolated AE (without hives) were mast cell mediated (16% were allergy related and 33% idiopathic), 36% were bradykinin induced (25% with C1 inhibitor deficiency, 11% drug related). Another study from a specialized AE center reported that 70% of AE without hives were mast cell mediated [10]. The distribution of our study is a little different. It can be explained by the different method of patient recruitment. The emergency doctors, who called the hotline, did it for the most serious AE and/or the most difficult diagnosis but also when the first line of treatment failed. We have not studied the calls of known patients of the CREAK (33 calls). In a previous study, we have demonstrated that the ED visits of HAE patients are reduced by a therapeutic education program that promote self-administration of specific treatment and call to hotline if needed [11,12]. These patients have direct access to the hotline in case of problems without going through a doctor or to ED.

The lack of follow up was a source of bias, especially for ACEi-AAE. The final diagnosis of ACEi-AAE must be done after 6 months to evaluate the AE incidence after the cessation of ACEi. The persistence of AE 6 months after, would reclassify patients to spontaneous MC-AE [13].

Approximately 50% of the patients had presented prior episodes of AE before the episode prompting the call. Our method of recruitment did not allow us to record the time since first episode and number of episodes. This and the fact that most calls originated from ED or intensive care units highlights that patients with AE consult various

doctors before the etiologic diagnosis can be made, often years after the first symptoms [14].

There was no statistically significant difference in the length of the episodes between the groups even if mast cell mediated AE are considered to be shorter than bradykinin mediated AE [15,16]. This may be explained by our measure of the episode length, only differentiating episodes less than 24 h, between 24 h and 72 h and over 72 h. ACEi-AAE Patients had statistically more AE localized to the tongue than patients in the MC-AE group, and less AE localized to the face. It is to be noted that almost every episode in this study concerned the face, tongue or ENT, and AE of the extremities or abdominal pain were almost inexistent, even if they are associated with mast cell and bradykinin mediated AE [15,16]. This may be explained by the identity of callers: almost 80% of calls originated from an ER or ICU, most patients with AE of the extremities or with abdominal pain will be considered less severe or may not even seek medical care. Only 4 patients in this study had no AE of the face-tongue or ENT. This study highlights the importance of suspicious ACEi-AAE in ED (49% of the calls). These patients had more frequent tongue and ENT localizations compared to MC-AE. The 7 ACEi-AAE patients versus 1 MC-AE were transferred to an ICU. The 2 hypotheses can be discussed. Emergency doctors used our guideline well and transfer suspicions of ACEi-AAE to ICUs as recommended (Figure 2). Or, ACEi-AAE are really more severe and required ICU as it has been shown before by Javaud et al. [17]. In the absence of clinical signs or paraclinical tests to help differentiate MC-AE versus ACEi-AAE, and considering the potential severity of BK-AE, the use of specific treatments (i.e. Icatibant) remains necessary, even though some of the patients merely present with MC-AE while under treatment by an ACEi [18,19].

All the doctors who called the hotline appreciate this tele-expertise a lot. In addition to providing rapid AE expertise, this service also allows to educate physicians in the management of AE irrespective of its origin.

Conflict of Interests

Bouillet L and Boccon-Gibod I received fees from Shire/Takeda, CSL Behring, Pharming, and Novartis.

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