

MISS MARION LEPELLEY (Orcid ID : 0000-0002-8506-8228)

DR LAURENCE BOUILLET (Orcid ID : 0000-0001-8245-4767)

Article type : Research Letter

Bradykinin mechanism is the main responsible for death by isolated asphyxiating angioedema in France.

Julia Crochet^a Marion Lepelley, DPharm^b Nassima Yahiaoui, DPharm^b Céline Vermorel, MSc^c Jean-Luc Bosson, MD, PhD^c

Pauline Pralong, MD^{a,d} Marie thérèse Leccia MD, PhD^{a,d} Laurence Bouillet, MD, PhD^{d,e}

^aDermatology Department, Grenoble Alpes University Hospital, France

^bPharmacovigilance Department, Grenoble Alpes University Hospital, France

^cPublic Health Department, Grenoble Alpes University Hospital, France

^dNational reference Center for Angioedema (CREAK), Grenoble Alpes University Hospital, France.

^eInternal Medicine Department, Grenoble Alpes University Hospital, France

Corresponding author: Laurence Bouillet

Internal Medicine Department

Grenoble Alpes University Hospital

CS 10217

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.13297

This article is protected by copyright. All rights reserved.

38043 Grenoble cedex 09, France

Tel: +33 476765565

Mail: lbouillet@chu-grenoble.fr

Keywords: angioedema, mortality, asphyxia, pathophysiology, histamine, mast cell, bradykinin,

Angioedema (AE) is a sudden localized, subcutaneous or submucosal, swelling due to one of two major possible mechanisms: mast cell induced (MC-AE) or bradykinin mediated (BkAE)^{1,2}. MC-AE may be allergic or non-allergic (mast cell degranulation non-specific to the antigen). BkAE may be hereditary, with (C1-INH-HAE) or without C1 inhibitor (C1-INH) deficiency. BkAE may also be acquired with C1-INH deficiency (C1-INH-AAE), complicating some blood diseases, dysimmunities or be iatrogenic, mainly due to angiotensin converting enzyme inhibitors (ACEi). While their clinical aspect is similar, their treatment is radically different. Some AE remain idiopathic, whether of bradykinin mediated, or mast cell induced secondary to unidentified mediators. There are no epidemiological data comparing AE mortality according to the pathophysiological mechanism. Our objective was to determine which etiology was the most common cause of death by asphyxia due to isolated head and neck AE.

Methods:

We have retrospectively collected all recorded cases of fatal isolated asphyxiating AE in France between 2000 and 2014 via death certificates registered by the Epidemiological Center for Medical Causes of Death (CépiDC) and the national pharmacovigilance database (BNPV). We excluded AE associated with another possible cause of death or with severe anaphylaxis (anaphylactic shock, asthma attack). Each case was evaluated and classified according to the most likely etiological mechanism: histamine, bradykinin, or indeterminate.

CépiDC uses the 10th revision of the International Classification of Diseases (ICD-10) for the analysis of death certificates. For each death, an initial cause and co morbidity are listed in chronological order, using a specific code and free text. We used the following codes: D841: complement deficit: C1 inhibitor deficiency, hereditary angioedema; J384: laryngeal oedema: glottis / subglottis / supraglottic; and T783: angioneurotic oedema, Quincke's oedema.

Concerning pharmacovigilance data, all deaths with mention of angioedema, Quincke's angioedema, angioneurotic edema, or laryngeal edema were selected. Anonymized reports included place, age, medical history, usual and introduced treatments, biological data and a summary of the episode leading to death.

Cases were independently classified by three experts: two physicians from the National Angioedema Reference Center (CREAK) and a Pharmacovigilance Unit pharmacist. In case of disagreement a consensus was found for each case through collegial discussion. Different factors were taken into consideration in determining the origin of the angioedema. Thus, among other things, we identified the following elements in favor of BK: ACEi intake, BkAE family background, B hemopathy context.... Factors in favor of MC-AE were a history of drug hypersensitivity and recent / semi-recent allergenic contact. The expert consensus proposed a likely cause of AE. Death rates were calculated using annual French demographic data between 2000 and 2014 from the National Institute for Demographic Studies. Lethality rates were estimated after a review of the literature, based on the different prevalence of BkAE or MC-AE, and considered to be stable over time (table I).

Results (table II):

Data from the CépiDC corresponded to 888 cases. 439 cases were excluded because the AE was an associated pathology but not a cause of death. 119 cases were not included due to possible other cause of death. Concerning pharmacovigilance data, among 202 cases reviewed, 185 cases were not included due to possible other cause of death. Five cases found in both registries (year, age and place

of death) were considered only once for the analysis. Of the 1090 AE analyzed (202 in BNPV and 888 in Cépidc bases), only 342 were deemed as being the cause of death.

The overall mortality rate was very low (0.36 deaths per million inhabitants). Deaths due to BkAE were more frequent, 0.14 /million compared to MC-AE , 0.09/millions. Based on lethality rates, BkAE has a 45-fold higher mortality risk than MC-AE. While MC-AE is the predominant cause of AE, it is rarely fatal (lethality 0.05 ‰). Deaths due to MC-AE were mainly related to an allergy. No case of chronic urticaria or mastocytosis was found among the cases studied but two cases from the pharmacovigilance database could evoke non-allergic MC-AE in view of delays of 2 hours between the allergenic exposure and the reaction.

Discussion:

This is the first national study of fatal cases of isolated head and neck AE. Our overall mortality rate is in line with the literature on this subject (0.30 deaths / million inhabitants between 1999 and 2010 in the United States). The main limitation of this study is the large number of cases of indeterminate AE (117). This is due to a possible lack of knowledge by physicians about the classification of AE, but also to an ICD-10 for AE that is unsuited to current scientific advances. Thus, the absence of a specific category for ACEi induced BkAE, could lead to these being classified artificially as AE with C1-inhibitor deficiency or even with allergic cause. Similarly, the absence of a specific category for spontaneous MC-AE in ICD-10 and the absence of obvious allergenic contact in 50% of the MC-AE in our study questions the mechanism of mast cell degranulation. Likewise, cases due to chronic spontaneous urticaria could have been underestimated: some cases of isolated angioedema without wheals can be part of chronic spontaneous urticaria.³

In order to improve the validity of future studies, a prospective study of severe cases of asphyxiating AE with systematic broad clinical and biological documentation (markers of allergy, mast cell degranulation, exploration of C1 inhibitor deficiency) should be considered. Updating of the ICD is planned for 2018. Basing ICD-11 on an exhaustive pathophysiological reasoned methodology for angioedema would allow for more accurate epidemiological answers. Our study provides reassuring evidence that non-allergenic MC-AEs are not deadly whereas BKAE are.

We thank Dr Alison Foote for translating and critically editing the manuscript.

In memory of Celine Villier.

Sources of funding: none

Conflict of Interest: none of the authors have a conflict of interest to declare

References:

1. Zuberbier, T., Aberer, W., Asero, R., Abdul Latiff, A. H., Baker, D., Ballmer-Weber, et al : The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. The 2017 revision and update. Allergy 2018: in press
2. Maurer, M., Magerl, M., Ansotegui, I., Aygören-Pürsün, E., Betschel, S., Bork, K., et al : The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. Allergy and WAO Journal 2018: in press.
3. Kim SJ, Brooks JC, Sheikh J, Kaplan MS, Goldberg BJ. Angioedema Deaths in the United States, 1979-2010. Ann Allergy Asthma Immunol 2014; 113: 630-34.

- Accepted Article
4. Bygum A. Hereditary Angio-Oedema in Denmark: A Nationwide Survey. *Br J Dermatol* 2009; 161: 1153-58.
 5. M. Cicardi et al., « Classification, Diagnosis, and Approach to Treatment for Angioedema: Consensus Report from the Hereditary Angioedema International Working Group », *Allergy*. 2014; 602- 16.
 6. Zanichelli A, Arcoleo F, Barca MP, Borrelli P, Bova M, Cancian M et al. A Nationwide Survey of Hereditary Angioedema Due to C1 Inhibitor Deficiency in Italy. *Orphanet J Rare Dis* 2015; 10: 11.
 7. Sánchez-Borges M, González-Aveledo LA. Angiotensin-Converting Enzyme Inhibitors and Angioedema. *Allergy Asthma Immunol Res*. 2010; 2: 195-8.
 8. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology of ACE Inhibitor Angioedema Utilizing a Large Electronic Health Record. *J Allergy Clin Immunol Pract*. 2017; 5:744-749.
 9. Cicardi M, Zanichelli A. Acquired Angioedema. *Allergy Asthma Clin Immunol*. 2010; 6:14.
 10. Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. Update of the Evidence Base: World Allergy Organization Anaphylaxis Guidelines. *World Allergy Organ J*. 2015; 8: 32.
 11. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The Diagnosis and Management of Anaphylaxis Practice Parameter: 2010 Update. *J Allergy Clin Immunol* 2010. 126: 477-480.
 12. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. *Clin Exp Dermatol*. 2010; 35: 869-73.

	Lifetime prevalence (per million inhabitants)	Level of evidence 1: many studies with similar data 2: few studies but concordant data between studies 3: low level of epidemiological precision / verification*	Source data
HAE	20	1	Prevalence of 1/50 000. ^{4,6}
ACEi induced AE	489	2	0.4 to 0.7% of patients exposed to ACEi will develop an AE. ^{7,8}
C1-INH-AAE	2	3	Estimated prevalence of 1/500 000. ⁹
Idiopathic non MC-AE	?		Rare.
Total BkAE	511 (3%)		
Allergic MC-AE	8800	3	Anaphylaxis affects 1.6% of the general population. ¹⁰ 50% to 60% of cases of anaphylaxis develop upper airway AE. ¹¹
Spontaneous MC-AE	7020	2	Spontaneous chronic urticaria affects about 1.8% of the general population and among them 33% have associated AE-urticaria and 6% have AE only. ¹²
Drug related non-allergic MC-AE	?		Absence of precise prevalence data on non-allergic AEs related to NSAIDs, contrast products, opiates, and antibiotics.
Total MC-AE	15820 (97%)		

Table 1: Prevalence of angioedema in the general population. Hypertension affects 31% of the French population (National Health Nutrition Study 2014) and 28.7% of hypertensive patients are treated with ACE inhibitors (French national social security data). The frequency of C1-INH-AAE has been evaluated by several authors, with one case of AAE for 8 to 10 cases of hereditary angioedema (HAE).

		BkAE	MC-AE	Indeterminate cause	All AE
Number of deaths 2000-2014 (% of total AE retained)		129 (37.7%)	96 (28.1%)	117 (34.2%)	342
Cases in CépiDC		117	93	115	
Cases in BNPV		12	3	2	
Mean number of deaths/year		9	6	8	23
Specific rate of deaths / million inhabitants (95%CI according to Poisson distribution)		0.14 (0.06 - 0.26)	0.09 (0.03 -0.21)	0.13 (0.05-0.25)	0.36 (0.23-0.54)
Lethality rate / 1000 patients with the studied types of AE (95%CI according to Poisson distribution)		0.270 (0.123-0.514)	0.006 (0.002-0.013)	-	-
Percentage of patients with at least one comorbidity		51 %	57 %	61 %	
Average age of patients at death		66	59	59	61
Percentage of men in each group		70 %	63 %	63%	65%
Etiology of cases		104 cases: C1-INH-HAE or C1-INH-AAE 23 cases: iatrogenic (ACEi, ARA) 3 cases associated with gammopathy	96 cases related to allergy. Allergens involved: - Unknown (50) - Medication (18) - Hymenoptera (16) - Other unspecified Chemical substance (8) - Food (4)	-	-

Table II: Deaths by bradykinin mediated angioedema, mast cell induced angioedema or indeterminate mechanism between 2000 and 2014 in France. The calculation of 95%IC assumed that death and lethality rates followed a Poisson law. Comorbidities were compared using a Chi² test: there was no significant difference between BkAE and MC-AE groups (p = 0.36). **CépiDC**: Epidemiological Center for Medical Causes of Death **BNPV**: national pharmacovigilance database.