

Epidemiological data of anaphylaxis in french emergency departments

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Abstract

Background: Although anaphylaxis has been pointed as a high priority public health issue in the allergy world community, morbidity and mortality epidemiological data are still not optimal. This first multi-centric epidemiological study performed in 7 French emergency departments for one year intended to map the key issues to substantiate the need for changes and support ongoing national and international efforts for better diagnosis, management and prevention of anaphylaxis.

Methods: This is a descriptive study using data routinely reported to French institutional administrative databases reported from 7 French public health institutions of the Lorraine region from January to December 2015, based on International Classification of Diseases (ICD)-10 pre-selected anaphylaxis-related codes and clinically validated as anaphylaxis cases.

Results: From the 202,079 ED admissions, 4,817 had ICD-10 anaphylaxis-related codes, 323 of those have been clinically validated as anaphylaxis cases. Although 45.8% presented severity criteria, adrenaline has been prescribed only in 32.4% of these cases. Overall 323 cases, 57.9% were subsequently referred to allergy work-up or evaluation (after or during hospitalization) and 17.3% received a prescription of auto-injectable adrenaline.

Conclusion: Taken the results of this study, there is an urgent and pressing need for improved public health initiatives regarding anaphylaxis recognition and treatment. Timely, we strongly believe that this document flags key problems, which may be managed in the forthcoming years by implementing national and international actions.

Key words: anaphylaxis, emergency, epidemiology, International Classification of Diseases (ICD), management

Resumen

Antecedentes: La anafilaxia es un problema prioritario de salud pública en la comunidad mundial alergológica. Sin embargo, los datos epidemiológicos disponibles de morbilidad y mortalidad son mejorables. Presentamos el primer estudio epidemiológico multicéntrico, realizado en siete departamentos de urgencias franceses durante un año, que tuvo como objetivo identificar de las cuestiones relevantes para lograr cambios en futuras estrategias, nacionales e internacionales, que deriven en un mejor diagnóstico, tratamiento y prevención de la anafilaxia.

Métodos: Se trata de un estudio descriptivo que utilizó la información proveniente de las bases de datos de siete instituciones francesas de salud pública, de la región de Lorena desde enero hasta diciembre de 2015. Se buscaron nomenclatura y códigos relacionados con la anafilaxia, de la Clasificación Internacional de Enfermedades (CIE-10), y los pacientes fueron validados clínicamente como casos de anafilaxia.

Resultados: De los 202,079 ingresos en urgencias, 4,817 tenían códigos relacionados con la anafilaxia CIE-10, 323 de los cuales se validaron clínicamente con el diagnóstico de anafilaxia. Aunque el 45,8% presentó criterios de gravedad, la adrenalina se prescribió solo en el 32,4% de estos casos. En total, 323 casos, el 57,9%, se remitieron posteriormente para un estudio o evaluación alergológica (después o durante la hospitalización) y el 17,3% recibió una receta de adrenalina autoinyectable.

Conclusión: Según los resultados de este estudio, existe una necesidad urgente e imperiosa de mejorar los planes de salud pública respecto al reconocimiento y tratamiento de la anafilaxia. Los problemas clave detectados en este trabajo, señalan el camino de la toma de decisiones e implementación de acciones de mejora, nacionales e internacionales, para una mejor atención de los pacientes con anafilaxia.

Palabras clave: anafilaxia, urgencias, epidemiología, Clasificación Internacional de Enfermedades (CIE), tratamiento.

BACKGROUND

Anaphylaxis is a recognized acute severe life-threatening generalized or systemic hypersensitivity reaction, which requires rapid recognition and treatment [1]. It may present as very different combinations of symptoms and apparently mild signs may unpredictably evolve into a fatal shock. Difficulty in the recognition of anaphylaxis is, in part, due to the variability of diagnostic criteria. As consequence, it leads in the delay of appropriate treatment, increasing the risk of death. Anaphylaxis is a recognized cause of death in all ages.

Although this condition has been pointed as a high priority public health issue in the allergy world community, morbidity and mortality epidemiological data are still not optimal. Reports of anaphylaxis incidence in emergency department (ED) have indicated rates ranging from 0.04 to 0.5% of visits [2-10]. This remarkable variability is related to different factors such as: (I) differences among populations, (II) characteristics of the ED Institutions, (III) difficulties on recognizing at-risk and anaphylactic patients, (IV) methodology applied to capture the rates.

Recent local French epidemiological data indicates an incidence of 32 per 100 000 person-years in hospitalized patients [11] and a national mortality rate of 0.83 (0.80-0.88) [12], but there are currently no epidemiological anaphylaxis morbidity studies in French EDs.

Ascertaining how anaphylaxis is diagnosed, and treated nationally and globally is an important preliminary step towards the development of public health strategic action plans in order to identify and solve key issues. We proposed a one-year multi-centric epidemiological study performed in 7 French EDs covering a population of 953,552 inhabitants in order to map the key issues to substantiate need for changes and support ongoing national and international efforts for better diagnosis, management and prevention of anaphylaxis.

METHODS

Data sources and case definition

This is a descriptive study using ED data routinely informed to French institutional administrative databases. French public health structure involving hospitals uses a system of coding alongside the length of hospital stay to determine the chargeable cost of care for each patient and for reimbursement. The coding system in use is the World Health

Organization's International Classification of Diseases (ICD), currently the ICD-10 [13]. The process of coding is by case note review, undertaken by professional coders. It relies on diagnosis, procedures and other events reported by the clinical team caring for the patient. The data are submitted to become part of national health statistics and are used for research and planning. French public health institutions serve as references for patients of the regions in which they located, therefore, all patients are generally addressed to these hospitals.

In this study, we evaluated data reported from 7 French public health institutions linked to University of the Lorraine urban region recorded from January to December 2015, extracted on January 2016. Lorraine is an administrative area of the northeast of France, counting with 32 public healthcare institutions of different complexities.

Of 202,079 ED admissions during the 2015-year, we accessed all consecutive files in which the primary cause of admission received anaphylaxis-related ICD-10 codes (Table 1). Incidence has been calculated based on the number of admissions during the 2015-year. Overall these 4,817 files, 323 (6.7%) cases have been retrospectively clinically validated as anaphylaxis cases. Clinical validation was performed by two independent allergists and based on the current accepted international diagnostic criteria and characterization of anaphylaxis [1,14,15]. Doubtful cases have been openly discussed with co-authors (Figure 1). We then reviewed the corresponding ICD-10 codes related to the clinical validated cases.

Reference population

The geographical regions were defined using the official French mapping used in 2014. Data was collected, anonymised after the institutions' CCTIRS (Advisory Committee on the Treatment of Information on Research in the field of Health) approval [16].

Statistical analysis

Data was analyzed using the LibreOffice and the EpiData softwares. Statistics descriptions included average, median and standard deviation calculations for quantitative variables, and frequencies and percentages for categorical variables. The group comparisons were made with the χ^2 test for categorical variables, and with Student's t-test for quantitative variables. An analysis of variance (ANOVA) was used to compare the averages of several samples. A value of $p < 0.05$ was considered significant.

RESULTS

Epidemiologic and clinical characteristics of the patients and results about management of the anaphylactic reactions are summarized in Table 2. For 2015, anaphylaxis was responsible for 0.16% ED admissions. Extrapolating to hospitals urban areas covered, the incidence was estimated at 34 per 100,000 person-years. Overall 323 patients, 67.2% were adults aged from 18 to 88.4 years and 32.8% children from 2 months to 18 years. The sex ratio was 1.32, with a higher proportion of males. Adults presented mainly drug-induced and insect sting related anaphylaxis whereas food has been pointed as the main trigger in the pediatric population (Table 2). No death has been reported. A history of previous episode of anaphylaxis has been found in 20.1% and a biphasic reaction in 5.0% of the patients. Total use of epinephrine was significantly higher in adults than in children ($P = 0.045$). Although 45.8% (148/323) of the subjects presented severe anaphylaxis (Ring & Messner grade ≥ 3), adrenaline has been prescribed only in 32.4% (48/148) of these cases, mostly by intravenous route (41.7%), and more often in children than in adults ($P = 0.02$). Children have been more referred to allergists and received a higher proportion of prescriptions than adults (Table 2). Serum tryptase has been measured in 12.7% of patients and 60.1% have been kept under hospital observation for less than 6 hours (median value 4.7 hours).

Overall 323 cases, 57.9% were subsequently referred to allergy work-up or evaluation (after or during hospitalization) and 17.3% received a prescription of auto-injectable adrenaline (Table 2). Twenty percent of the subjects experienced more than one episode of anaphylaxis even after the allergological diagnosis established, 37% with exposure to food allergens and 22% after drug intake.

Some cofactors have been identified as significantly ($P < 0.05$) associated with more severe (grade ≥ 3) anaphylactic episodes, such as a concomitant asthma in children (OR 2.37, 95% CI 1.04-5.38) and use of one or more of the following drugs: β -blockers, aspirin and non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor antagonists, proton pump inhibitors, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists in adults (OR 2.18, 95% CI 1.20-3.94). Clinical presentations were influenced by specific factors: concomitant asthma was associated with more lower respiratory symptoms (OR 2.26, 95% CI 1.28-3.98), cardiovascular disorders with cardiovascular injury (OR 2.19, 95% CI 1.06-4.52), and food trigger with gastro-intestinal manifestations (OR 1.83, 95% CI 1.15-2.92), $P < 0.05$ for all.

From the 323 cases validated as anaphylactic cases, only 14.3% presented direct anaphylaxis corresponding ICD-10 codes (Figure 1).

DISCUSSION

This first study presenting morbidity epidemiological data and characteristics of how anaphylaxis is managed in French EDs highlighted the need to implement harmonization of knowledge related to anaphylaxis management. The awareness of anaphylaxis as a life-threatening medical condition has been increasing among different specialties and the publications over the last years have indicated that it is not an uncommon condition as previously perceived. However, most of the publications so far considered all the degrees of severity of anaphylaxis and the severe forms may still well be considered as rare diseases [17]. We here demonstrated that anaphylaxis was responsible for 0.16% ED admissions, with an incidence estimated at 34 per 100,000 person-years.

Although injectable adrenaline is currently listed in the World Health Organization (WHO) list of essential drugs for the treatment of anaphylaxis, remarkable in the present study was the low number of adrenaline prescribed even in severe cases [18]. This data is aligned with most of recent published data in the field [2-10]. Additionally, a relevant number of these cases were hospitalized or kept under observation for a shorter period of time than recommended [15].

In contrast to most of international recommendations [14], we observed large percentage of intravenous adrenaline use, which possible serious complications such as acute pulmonary edema, arrhythmia, and acute coronary events among others. In addition, we demonstrated reduced proportion of referral to allergists and lack of prescription of epinephrine autoinjectors. We believe that these findings may be related with the uncertainty of physicians about the diagnosis of anaphylactic cases, defined based on indirect ICD-10 codes for anaphylaxis. The recent recognition of the allergy specialty as a full discipline opens the opportunity of bilateral collaboration with other specialties, which may support increasing awareness regarding management of anaphylactic patients.

Striking was the number of patients who presented a second episode of anaphylaxis even with the allergological diagnosis. This fact calls for the need of strengthening awareness among patients and carriers in order to avoid re-exposure to known triggers. Educational efforts will also help to decrease the under-recognition of anaphylaxis by patients, caregivers, and health professionals, health authorities and governments and have

been the main aim of allergy academies by promoting education programs and publications in the field [1, 14,15,19-22].

Serial serum (or plasma) levels of tryptase collection are recommended to guide the diagnosis of anaphylaxis or to exclude mast cell disorders, which can mimic anaphylaxis. However, it has been collected in a limited number of severe reactions, calling for the need of systematization of an anaphylaxis action plan. Timely, national and international guidelines have been built to implement these gaps [14,23-25].

A recognized reason for under-notification or under-estimation of anaphylaxis is the difficulty of coding anaphylaxis fatalities under the WHO ICD system. Limited numbers of ICD-10 codes are considered valid for specific anaphylaxis morbidity and mortality [8], as demonstrated through the patients diagnosed by direct (46 cases) and indirect (277 cases) ICD-10 codes for anaphylaxis (Figure 1). For this reason, we included additional codes related to manifestations and causes that could resemble or evoke anaphylaxis or even allergic reactions (Table 1). Over the last 5 years, a strategic international action plan supported by the Joint Allergy Academies and the ICD WHO governance [11,17,18,26-31] took place to update the classifications of allergic conditions for the new ICD edition. These efforts have resulted in the construction of the new “Allergic and hypersensitivity conditions” section in the ICD-11 [28,32], with a subsection addressed exclusively to anaphylaxis, which will support better morbidity and mortality statistics.

Aligned to the recent international achievements, are all the efforts made since 2014 to recognize Allergy as a full academic specialty in France. In a higher perspective, this academic move will permit a better formation of health professionals in the field and supports quality management of allergic patients. Anaphylaxis, as well as other allergic and hypersensitivity conditions, are systemic disorders which require a multi-disciplinary approach [17]. This medical specialization will allow bilateral dialog and strengthen collaborations among specialties by increasing scientific consistence and awareness.

This study is the first epidemiologic report of anaphylaxis in EDs in France, and highlights the regional differences of anaphylaxis incidence and management. Although the retrospective nature of the study may hamper the diagnosis of anaphylaxis, all the cases have been manually clinically validated in order to reduce doubtful cases. Another known limitation is the number of ED institutions taking part of this study and the size of the geographic area studied, which may have influence in the epidemiological findings. However, with the presented results, we reached the aim of deliberating the national and

international efforts for the better diagnosis and management of anaphylaxis. Broader studies are scheduled in order to increase our knowledge regarding epidemiological quality data and to support advances and use of the new classification of allergic and hypersensitivity conditions. We intend to support the implementation process of the ICD-11 in order to reach more accurate and comparable anaphylaxis morbidity data.

Taken the results of this study, there is an urgent and pressing need for improved public health initiatives regarding anaphylaxis recognition and treatment. The data here presented are convergent with the finding of the European Anaphylaxis registry, which concludes that despite clear recommendations, only a small proportion of anaphylaxis incidents are treated with epinephrine [33]. Timely, we strongly believe that this document flags key problems, which may be managed in the forthcoming years by implementing national and international actions. Strategies to overcome the key barriers of the anaphylaxis care should be based on bilateral partnership among allergists and emergency physicians.

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CONFLICT OF INTERESTS:

The authors declare that they do not have conflict of interests related to the contents of this article.

CONTRIBUTIONS:

All authors contributed to the paper. The first and last authors (Jeremy Corriger and Luciana Kase Tanno) contributed to the construction of the document (designed the study, analyzed and interpreted the data, and wrote the manuscript). Etienne Beaudouin and Pascal Demoly contributed interpreting the data and reviewing the manuscript. The co-authors helped with the literature review, in the discussion and with the revision of the document.

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Table 1: Corresponding International Classification of Diseases (ICD)-10 anaphylaxis-related codes used in the first step of the cases selection (n=95)

ICD-10 codes (2016)		Description
Category	Extension	
D69	.0	Allergic purpura
H10	.1, 3, 9	Conjunctivitis
I46	.0, 9	Cardiac arrest
I95	.8	Other hypotension
J30	.1 – 4	Allergic rhinitis
J38	.4, 5	Oedema of larynx and laryngeal spasm
J39	.3	Upper respiratory tract hypersensitivity reaction
J45	.0, 1, 8, 9	Asthma
J46	.X	Status asthmaticus and acute severe asthma
J67	.8, 9	Hypersensitivity pneumonitis due to other or unspecified organic dust
K52	.2	Allergic and dietetic gastroenteritis and colitis
K90	.4	Malabsorption due to intolerance or hypersensitivity
L03	.9	Cellulitis, located oedema or erythema
L20	.8, 9	Atopic dermatitis
L23	.0 – 9	Allergic contact dermatitis
L24	.0 – 9	Irritant contact dermatitis
L25	.0 – 5, 8, 9	Unspecified contact dermatitis
L27	.0 – 2, 8, 9	Dermatitis or skin eruptions due to substances taken internally, drugs and medicaments
L30	.8, 9	Dermatitis and eczema
L50	.0 – 9 (excl 3, 7)	Urticaria
L53	.0, 9	Toxic or unspecified erythema
L56	.0 – 3	Drug hototoxic or photoallergic responses, photocontact dermatitis and solar urticaria
M31	.0	Hypersensitivity angitis
M36	.4	Arthropathy in hypersensitivity reactions
O29	.3	Toxic reaction to local anaesthesia during pregnancy
O74	.4	Toxic reaction to local anaesthesia during labour and delivery
O89	.3	Toxic reaction to local anaesthesia during puerperium
R21	.X	Rash and other non specific skin eruption
R60	.1, 9	Generalized or unspecified oedema
T78	.0	Anaphylactic shock due to adverse food reaction
T78	.1	Other adverse food reactions
T78	.2	Anaphylactic shock, unspecified
T78	.3	Quincke oedema
T78	.4	Allergic reaction, unspecified
T80	.5	Anaphylactic shock due to serum
T80	.6	Other serum reactions
T81	.1, 6	Shock or acute reaction resulting from a procedure or a substance left during a procedure
T88	.6	Anaphylactic shock due to adverse effect of correct drug properly administered
Z01	.5	Diagnostic skin and sensitization tests (allergy tests)
Z51	.6	Desensitization to allergens

Table 2: Features and demographic data of anaphylaxis cases

DEMOGRAPHIC DATA OF ANAPHYLAXIS CASES	CHILDREN (< 18 years) N = 106 (32.8%)	ADULTS (≥ 18 years) N = 217 (67.2%)	TOTAL (0 – 88 years) N = 323 (100.0%)	P-value*
GENDER				
Male	65 (61.3%)	119 (54.8%)	184 (57.0%)	0.27
Female	41 (38.7%)	98 (45.2%)	139 (43.0%)	
MANIFESTATIONS				
Cutaneous	95 (89.6%)	202 (93.1%)	297 (92.0%)	0.28
Respiratory	69 (65.1%)	141 (65.0%)	210 (65.0%)	0.98
Upper airway	51 (48.1%)	91 (41.9%)	142 (44.0%)	0.29
Lower airway	45 (42.5%)	93 (42.9%)	138 (42.7%)	0.95
Cardiovascular and/or loss of consciousness	36 (34.0%)	98 (45.2%)	134 (41.5%)	0.06
Gastro-intestinal	47 (44.3%)	60 (27.6%)	107 (33.1%)	0.002
BIPHASIC REACTION	8 (7.5%)	8 (3.7%)	16 (5.0%)	0.13
SEVERITY**				
Grade I	22 (20.8%)	47 (21.7%)	69 (21.4%)	0.85
Grade II	37 (34.9%)	69 (31.8%)	106 (32.8%)	0.58
Grade III	47 (44.3%)	99 (45.6%)	146 (45.2%)	0.83
Grade IV	0 (0.0%)	2 (0.9%)	2 (0.6%)	0.32
COFACTORS				
Asthma	36 (34.0%)	25 (11.5%)	61 (18.9%)	< 0.001
Cardiovascular disease	3 (2.8%)	31 (14.3%)	34 (10.5%)	0.002
Alcohol intake	0 (0.0%)	11 (5.1%)	11 (3.4%)	0.002
Associated drugs	1 (0.9%)	65 (30.0%)	66 (20.4%)	< 0.001
β-blockers	0 (0.0%)	23 (10.6%)	23 (7.1%)	< 0.001
NSAIDs or Aspirin	0 (0.0%)	29 (13.4%)	29 (9.0%)	< 0.001
ACEIs or ARBs	0 (0.0%)	39 (18.0%)	39 (12.1%)	< 0.001
PPIs	1 (0.9%)	20 (9.2%)	21 (6.5%)	0.005
ETIOLOGY				
Drugs	7 (6.6%)	76 (35.0%)	83 (25.7%)	< 0.001
Beta lactams	2 (1.9%)	37 (17.1%)	39 (12.1%)	< 0.001
Other antibiotics	0 (0.0%)	8 (3.7%)	8 (2.5%)	0.045
NSAIDs	2 (1.9%)	7 (3.2%)	9 (2.8%)	0.49
Radiocontrast agents	0 (0.0%)	14 (6.4%)	14 (4.3%)	0.008
Other or unidentified	3 (2.8%)	10 (4.6%)	13 (4.0%)	0.45
Food	82 (77.4%)	55 (25.3%)	137 (42.4%)	< 0.001
Peanut and nuts	29 (27.3%)	9 (4.1%)	38 (11.8%)	< 0.001
Hen egg	6 (5.7%)	1 (0.5%)	7 (2.1%)	0.003
Cow milk	9 (8.5%)	0 (0.0%)	9 (2.8%)	< 0.001
Fish and meat	4 (3.8%)	5 (2.3%)	9 (2.8%)	0.45
Shellfishes	2 (1.9%)	17 (7.8%)	19 (5.9%)	0.03
Other or unidentified	32 (30.2%)	23 (10.6%)	55 (17.0%)	< 0.001

Insect sting	10 (9.4%)	65 (30.0%)	75 (23.2%)	< 0.001
Undetermined	4 (3.8%)	21 (9.7%)	25 (7.8%)	0.06
Other	3 (2.8%)	0 (0.0%)	3 (0.9%)	0.01
PREVIOUS HISTORY OF ANAPHYLAXIS	28 (26.4%)	37 (17.1%)	65 (20.1%)	0.049
SERUM TRYPTASE MEASUREMENT	8 (7.5%)	33 (15.2%)	41 (12.7%)	0.05
TREATMENT				
Use of adrenaline				
<u>Administration route</u>	12 (11.3%)	44 (20.3%)	56 (17.3%)	0.045
Intravenous				
Intramuscular	2 (1.9%)	20 (9.2%)	22 (6.8%)	0.01
Subcutaneous	5 (4.7%)	4 (1.9%)	9 (2.8%)	0.14
Inhaled	0 (0.0%)	5 (2.3%)	5 (1.5%)	0.12
Unknown	4 (3.8%)	7 (3.2%)	11 (3.4%)	0.07
<u>By severity**</u>	1 (0.9%)	8 (3.7%)	9 (2.8%)	0.16
Grade I				
Grade II	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Grade ≥ III	3 (8.1%)	5 (7.2%)	8 (7.5%)	0.87
Systemic antihistamine	9 (19.1%)	39 (38.6%)	48 (32.4%)	0.02
Systemic corticosteroid	89 (84.0%)	195 (89.9%)	284 (87.9%)	0.13
	91 (85.8%)	184 (84.8%)	275 (85.1%)	0.80
HOSPITALIZATION	31 (29.2%)	15 (6.9%)	46 (14.2%)	< 0.001
OBSERVATION PERIOD AT THE ED				
< 6 hours	88 (83.0%)	149 (68.7%)	237 (73.4%)	
> 6 hours	18 (17.0%)	68 (31.3%)	86 (26.6%)	0.006
REFERRED TO THE ALLERGIST	78 (73.6%)	109 (50.2%)	187 (57.9%)	< 0.001
PRESCRIPTION OF AUTO-INJECTABLE ADRENALINE	26 (24.5%)	30 (13.8%)	56 (17.3%)	0.02

N for the number of patients, NSAIDs for non-steroidal anti-inflammatory drugs, ACEIs for angiotensin-converting enzyme inhibitors, ARBs for angiotensin-2 receptor blockers, PPIs for proton pump inhibitors

** P-value for test of equality of proportions*

***Ring & Messmer classification*

Figure 1: Flow chart: patients selection and inclusion applying the International Classification of Diseases (ICD)

