ORIGINAL ARTICLE

Anaphylaxis trend before and during pandemic: COVID-19 did not affect anaphylaxis frequency

Anaphylaxis frequency was not affected by COVID-19

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ABSTRACT

Background. Data on epidemiology of anaphylaxis are difficult to record. During the lockdown in 2020-2021 due to Coronavirus disease 2019 (COVID-19), referrals to Emergency Department (E.D.) reduced. The aims of the study are to determine anaphylaxis frequency before and during COVID-19 pandemic and risk factors for severity. **Methods**. Clinical records from a general E.D. of Milan in Italy were retrospectively evaluated before (2018-2019) and during the COVID-19 pandemic (2020-2021) analyzing demographic data, comorbidities, chronic therapies, causes, severity and adrenaline use. **Results**. The frequency of anaphylaxis remained stable (120/104129 = 0.12% in 2018-2019; 72/66720 = 0.11% in 2020-2021). No differences in the occurrence of anaphylaxis were found in sex and mean age. The main causes of anaphylaxis were food (2018-2019: 53% vs 2020-2021: 51%) and drugs (2018-2019: 27% vs 2020-2021: 33%). Hymenoptera stings had a low occurrence and unidentified trigger was about 15% in each period. The severity of anaphylaxis had a similar distribution in the two periods. Gender and cardiovascular diseases did not influence the severity, instead a positive correlation was found in age over 50 yo ($p<0.001$). Angiotensin II receptors blockers, β-blockers, diuretics and proton pump inhibitors were associated with increasing severity ($p<0.01$). Adrenaline administration was similar in the two periods. **Conclusions**. Anaphylaxis frequency was not affected by the COVID-19 pandemic. Food anaphylaxis remained the most important cause in the urban area. The severity of anaphylaxis was affected by ageing and some chronic therapies, which indirectly point out the role of chronic diseases in the clinical presentation.

KEY WORDS

Anaphylaxis; anaphylaxis epidemiology; anaphylaxis frequency; anaphylaxis risk factors; COVID-19.

INTRODUCTION

Anaphylaxis is a serious and potentially life-threatening allergic reaction.[1] In many instances, an IgE-mediated mechanism can be detected, sometimes other not completely understood mechanisms. The most frequent elicitors are food, insect stings and drugs, depending on age and geographical location. Co-factors as exercise, non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol are often involved. Anaphylaxis is defined idiopathic when no trigger can be identified and a clonal mast cell disorder has been excluded.[2]

World Allergy Organization (WAO) guidelines diagnostic criteria define anaphylaxis on the presence of typical skin symptoms and significant symptoms from at least one other organ system (respiratory, cardiovascular or gastrointestinal) with acute onset. Anaphylaxis can also be diagnosed after exposure to a known or highly probable allergen for that specific patient with acute respiratory and/or cardiovascular compromise, even in the absence of cutaneous involvement.[1]

The clinical history plays a crucial role in diagnosing anaphylaxis, identifying causes and assessing risk factors.[3] Diagnosis can be supported by elevation of serum total tryptase concentration of 120% of baseline plus 2 ng/mL, even if an increase is not always detectable.[4] However, such biomarker is not available in all Emergency Department (E.D.).

The global incidence of anaphylaxis varies from 1.5 to 103 episodes per 100,000 person-years, with geographic differences worldwide. The estimated lifetime prevalence is between 0.05 and 2 % in USA while it is 3 % in Europe.[5] The variability may be explained by differences in inclusion criteria due to the absence of a univocal definition.[6]
In Italy, neither national nor regional registers of all anaphylaxis incidence do exist. Only a descriptive italian study analyzed data recorded in the National Register of Causes of Death in the years 2004-2016 and reported anaphylaxis-related mortality of 0.51 per million population per year.[7]
The major aim of this study was to evaluate the trend of anaphylaxis frequency, clinical characteristics and comorbidities in patients admitted to the E.D. of a general hospital in Milan before and during the SARS-CoV2 pandemic.

MATERIALS AND METHODS

We retrospectively analyzed records of patients discharged from the E.D. of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan with a diagnosis of allergic or anaphylactic reaction, comparing the period 2018-2019 to the COVID-19 pandemic (2020-2021).
Written informed consent to access personal and clinical data was obtained in the E.D. as soon as possible and within the limits of care needs. Ethical approval was not required for this study involving anonymized clinical records collected retrospectively and analyzed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.
Records regarding adult (18+ yo) patients were extracted if their post-discharge diagnosis reported any of the following International Classification of Diseases, 9 th revision (ICD-9) codes: 9950 (Other anaphylactic reaction), 99560 to 69 (Food related anaphylactic reactions), 9953 (Allergy, unspecified), 99527 (Drug allergy NEC). Anaphylaxis was confirmed if the clinical presentation fulfilled the WAO diagnostic criteria.[1]
We evaluated demographic data, cardiovascular and allergic comorbidities, causes of anaphylaxis, chronic therapies (which could worsen the reaction presentation), severity grade according to the WAO classification, risk factors and treatments.
The frequency of anaphylaxis and other selected variables between the two two-year periods were compared using chi-squared test (for categorical variables) or Wilcoxon rank-sum test (for quantitative variables). Analyses were performed with Stata 18 (StataCorp. 2023).

RESULTS

Anaphylaxis frequency
In the pre-COVID era (2018-2019), 104129 patients were referred to E.D., while, during the COVID pandemic (2020-2021), admissions were 66720, with a 36% reduction.
The frequency of suspected allergic reactions was similar in both periods (2018-2019: 787 out of 104129 = 0.76% vs 2020-2021: 482 out of 66720 = 0.72%, p=0.43).
There was no difference in the frequency of anaphylaxis among the total number of E.D. admissions in the pre-COVID and Covid pandemic (2018-2019: 120 out of 104129 = 0.12% vs. 2020-2021: 72 out of 66720 = 0.11%, p=0.65).

Demographic and clinical data in cases of anaphylaxis
There was no difference between males and females in the occurrence of anaphylaxis in the two-year periods (2018-2019: 71 female out of 120 = 59% and 49 male out of 120 = 41% vs 2020-2021: 42 female out of 72 = 58% and 30 male out of 72 = 42%, p=0.91).
No age difference was observed in the two periods: the mean age in the pre-COVID period was 45.3 yo, while in the COVID period it was 42.6 yo (p=0.50).
In the COVID period there were more atopic patients (suffering from asthma, allergic rhinitis or food allergy) in the anaphylaxis group (39 out of 72 = 54%) than in the pre-COVID period (17 out of 120 = 14%), p <0.001.
Consistently with these data, in the COVID period more patients were on inhalator therapy (2018-2019: 2 out of 120 = 1.6% vs 2020-2021: 8 out of 72 = 11.1%, p=0.004) and antihistamine therapy (2018-2019: 1 out of 120 = 0.8% vs 2020-2021: 5 out of 72 = 6.9%, p=0.02). In patients with anaphylaxis on antihypertensive therapy, no differences were detected in the two periods for each antihypertensive class such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptors blockers (ARBs), β-blockers, calcium channel blockers (CCBs), diuretics and alpha blockers.

Causes of anaphylaxis

A similar distribution in the culprits was observed in the comparative analysis of anaphylaxis triggers between 2018-2019 and 2020-2021: food was the leading cause of anaphylaxis in both the biennia (2018-2019: 64 out of 120 = 53% vs 2020-2021: 37 out of 72 = 51%, p=0.79), the second frequent trigger were drugs (2018-2019: 33 out of 120 = 27% vs 2020-2021: 24 out of 72 = 33%, p= 0.66), Hymenoptera stings and other triggers had a similar low occurrence. Unidentified trigger remained a cause of anaphylaxis in about 15% of cases in each period.

Severity grading of anaphylaxis

The severity of anaphylaxis had a similar distribution in the two-year periods (p=0.27). In 2018-2019, out of a total of 120 reactions, 61 (50.8%) were grade 3, 26 (21.7%) grade 4, and 33 (27.5%) grade 5. In 2020-2021, out of a total of 72 anaphylaxis, 42 (58.3%) were grade 3, 9 (12.5%) grade 4, and 21 (29.2%) grade 5.

No differences were found in the severity grading distribution considering the trigger of anaphylaxis, except for food when more severe reactions in the pre-COVID biennium were recorded. (Table I)

During the pre-COVID era (2018-2019), 28 out of 120 patients with anaphylaxis (23.3%) experienced hypotension, compared to 17 out of 72 (23.6%) in the pandemic period (2020-2021), p=0.96.

Furthermore, in the pre-COVID years (2018-2019), 11 out of 120 patients (9.2%) experienced loss of consciousness, while 6 out of 72 (8.3%) during the pandemic period (2020-2021), p=0.84.

Anaphylaxis risk factors

Gender, cardiovascular diseases, food allergy, drug allergy and Hymenoptera venom allergy, did not influence the severity of anaphylaxis.

The increase in anaphylaxis severity was correlated with an increase in the mean age (grade 3: mean age 39, grade 4: mean age 48, grade 5: mean age 52, p<0.001). In detail, out of 192 events, anaphylaxis was less severe in the 122 patients younger than 50 yo (64.8% grade 3, 16.4% grade 4, 18.9% grade 5) than in those aged 50 or more years (34.3% grade 3, 21.4% grade 4, 44.3% grade 5), p<0.001.

Among ongoing therapies ACEIs and CCBs did not show any influence on severity grading (p=0.10).

In contrast the use of angiotensin II receptors blockers (ARBs), β-blockers, diuretics and proton pump inhibitors (PPIs) were associated with increasing level of severity (p<0.01). To a lesser extent alpha blockers (p=0.02), statins (p=0.025) and antiplatelets (p=0.018) worsened the severity of anaphylaxis.

Factors such as physical exercise, acute infection, emotional stress, and NSAIDs were not correlated with the severity of anaphylaxis. Also, no correlation is found between trigger of anaphylaxis and severity grading.

Anaphylaxis treatment

In the pre-COVID-19 period 82 patients out of 120 (68%) were treated with adrenaline, during the COVID period 43 out of 72 (60%), p=0.22, 27 out of 120 patients (23%) required airway support in the pre-COVID period (2018-2019), while 34 out of 72 (10%) during the pandemic period (2020-2021), p= 0.025.

DISCUSSION AND CONCLUSIONS

Between the pre-COVID period and the pandemic, the occurrence of allergic reactions remained stable, with a stable female prevalence and mean age. Antihypertensive chronic therapies were homogeneous in the two series, but in the pandemic there were more atopic patients, probably because during this period more attention was paid to respiratory diseases.

Despite a general reduction in E.D. visits and probably also in anaphylaxis, the COVID pandemic did not affect the frequency of anaphylaxis nor the severity of reactions. These data must be interpreted taking into account the lower exposure during COVID-19 period to various allergenic sources due to restriction measures.

Compared to a previous study conducted in the same hospital in 1997-1998 [8] there were both a decrease in the number of allergic reactions (3.2% vs 0.7% in the present study) and in the prevalence of anaphylaxis (0.3% vs 0.1%). A possible explanation could be that the mean age has increased (38 yo in 1997-1998, 45 in 2018-2019 and 42 in 2020-2021): food still remained the most common trigger but it is a less frequent elicitor of anaphylaxis in elderly than insect venoms and drugs [9], in fact these triggers were less represented in our population. Although there is evidence that anaphylaxis prevalence has been increasing in the past decades especially in children under 5 yo [10], in our study we found only a slight decrease in the frequency of anaphylaxis in adults.

The risk and severity of anaphylaxis was not affected by gender, though there was a general female predominance both in suspected allergic reactions and anaphylaxis. This could be explained by the fact that during adulthood women are more affected than men in many of allergic diseases such as food allergy [11], drug allergy [12] and asthma [13].
The clinical history enabled us to formulate an almost certain diagnosis. The main causes of anaphylaxis were similar in the two two-year period: food and drugs were the most common triggers. During the pandemic there was a slight decrease in unidentified triggers, probably due to an improvement in the awareness of anaphylaxis. Even if Hymenoptera venom is a frequent elicitor of anaphylaxis[14], in our study it represents a minor elicitor, probably due to the downtown setting of the hospital and consequently less common exposure.
The strict correlation between age and anaphylaxis severity seems to be in accordance with the observation that anaphylaxis tends to be more severe in the elderly. [9]
Analyzing possible risk factors for a severe reaction, we also found a correlation with the increase of mean age and also with several ongoing therapies, particularly antihypertensive and cardiovascular molecules (ARBs, β-blockers, diuretics, alpha blockers, statins, antiplatelets). ACEIs and CCBs showed only a positive trend with the severity of anaphylaxis. Nevertheless, sex and a documented cardiovascular diseases did not worsen the reactions. In recent years beta-blockers and ACEIs were more often associated with serious reactions compared to other cardiovascular molecules. [15] However, no correlation was found between ACEIs and β-blockers therapies and severity of anaphylaxis by Hymenoptera venom allergy.[16] In our study, ageing and chronic therapies indirectly testify the role of chronic cardiovascular disease in the severity of anaphylaxis reactions. [17,18]
Concerning other common chronic therapies, PPIs seemed to worsen the reactions, probably due to its frequent use in patient taking antiplatelet therapy. It was not possible to evaluate if PPI was directly involved in food allergic ones. [19]
The appropriate treatment with adrenaline was similarly administered before and during the pandemic in agreement with a similar frequency reported. [20] Some patients, stable at the arrival may not be treated by adrenaline in case of complete symptoms resolution. [21]
One of the limits of this analysis is the underestimation of anaphylaxis due to possible misdiagnosis and misclassification made in the E.D. [22] Especially in a crowded E.D., some physicians could be induced to use other generic codes given the complexity of ICD-9 coding. Other causes of underestimation could be the undefined catchment area of the hospital and non-identified community cases.
No European or global anaphylaxis registries was able to comprehensively register all community cases due to various difficulties. In Italy there is a lack of updated data on regional or national incidence of anaphylaxis. [23] Our results suggest that the anaphylaxis frequency in E.D. was not affected by the COVID-19 pandemic. Food anaphylaxis remained the most important cause, at least in our urban area. Ageing and some chronic therapies, mostly cardiovascular molecules, are risk factors for a more severe reaction.
In the future, a national or regional study should be designed to register every event from E.D., emergency services and outpatient medical records to discover the real incidence and burden of anaphylaxis.

FUNDINGS

This study was partially funded by Italian Ministry of Health, Current research IRCCS

AUTHORS' CONTRIBUTIONS

AS: study conceptualization and design, interpretation of the data, writing; AF,VL: acquisition of the data, DC: statistical expertise, analysis; VP, AJ, VM: drafting of the manuscript; FR: editing and critical revision of the manuscript for important intellectual content, NM: supervision, acquisition of funding.

CONFLICT OF INTERESTS

None of the authors have a conflict of interest to disclose

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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		2018-2019			tot	2020-2021			tot	p value
	Severity grade	3	4	5		3	4	5		
Causes	Food	32 (50%)	18 (28.1%)	14 (21.9%)	64	28 (75.7%)	4 (10.8%)	5 (13.5%)	37	0,035
	Drugs	17 (51.5%)	3 (9.1%)	13 (39.4%)	33	10 (41.6%)	3 (12.5%)	11 (45.8%)	24	0.750
	Hymenoptera sting	2 (40%)	0 (0%)	3 (60%)	5	1 (100%)	0 (0%)	0 (0%)	1	0.273
	Latex	1 (100%)	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	0 (0%)	0	
	Unidentified	9 (52.9%)	5 (29.4%)	3 (17.6%)	17	3 (30%)	2 (20%)	5 (50%)	10	0.203

Table I. Severity grading of anaphylaxis by triggers in the Pre-COVID period and during the COVID period.