



Epidemiology of anaphylaxis in Brazil: The Brazilian Registry of Anaphylaxis (RBA) of the Brazilian Association of Allergy and Immunology (ASBAI)

Epidemiologia da anafilaxia no Brasil: Registro Brasileiro de Anafilaxia (RBA) da Associação Brasileira de Alergia e Imunologia (ASBAI)

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ABSTRACT

Introduction: Anaphylaxis is a life-threatening, acute, severe multisystem allergic reaction. There is little data on its epidemiology in Brazil. The Brazilian Anaphylaxis Registry of the Brazilian Association of Allergy and Immunology (RBA-ASBAI) was devised to expand knowledge about anaphylaxis in Brazilian individuals.

Methods: Cross-sectional observational study using an online questionnaire to collect data on demographics, suspected triggers, clinical manifestations, treatment during the reaction, diagnostic workup, and post-reaction counseling in patients who have experienced an anaphylactic reaction. **Results:** Between June 2021 and April 2023, 237 patients were included (131 female): 99 children/adolescents (<18yo), 127 adults (18-64yo), and 11 older adults (65-77yo). There was a male predominance in the pediatric group (55.5%), while females were predominant among adults (64.5%). The median age was 22 years (range, <1 to 77). The most frequent clinical manifestations were cutaneous

RESUMO

Introdução: A anafilaxia é uma reação alérgica multissistêmica grave, de início agudo e potencialmente fatal. Poucos são os dados sobre sua epidemiologia no Brasil. O Registro Brasileiro de Anafilaxia da Associação Brasileira de Alergia e Imunologia (RBA-ASBAI) teve como objetivo ampliar o conhecimento sobre anafilaxia em indivíduos brasileiros. **Métodos:** Estudo observacional transversal com questionário *online* sobre dados demográficos, desencadeantes suspeitos, manifestações clínicas, atendimento durante a reação, investigação diagnóstica e aconselhamento após a reação de pacientes que experimentaram uma reação anafilática. **Resultados:** Entre junho/2021 e abril/2023, foram incluídos 237 pacientes (131 femininos): 99 crianças/adolescentes; 127 adultos e 11 idosos. Houve predomínio de meninos entre crianças/adolescentes (55,5%), e de mulheres entre os adultos (64,5%), e mediana de idade de 22 anos (< 1 a 77 anos). As manifestações cutâneas (92,8%) foram as mais frequentes, seguidas pelas respi-

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(92.8%), followed by respiratory (70.1%), gastrointestinal (52.3%), neurological (36.3%), and cardiovascular (35.3%). The most common triggers were foods (43.0%), drugs (26.2%), venoms (21.6%), and latex (2.5%). Foods (milk, egg, peanuts/tree nuts) predominated among children, versus drugs (mostly nonsteroidal anti-inflammatory drugs and antibiotics) among adults. Regarding treatment, 61.1% received epinephrine (52.7% by a healthcare professional and 8.4% via epinephrine auto-injector [EAI]). One teenager (12yo) died due to a bee sting. Most patients received a written emergency plan (78.1%) and were taught how to use the EAI (70%). **Conclusion:** Foods were the most common triggers of anaphylaxis among Brazilian children and adolescents, while drugs predominated among adults. Epinephrine continues to be underused, highlighting the need for greater awareness of proper treatment of anaphylaxis.

Keywords: Anaphylaxis, food hypersensitivity, drug hypersensitivity, venom hypersensitivity, epinephrine.

ratórias (70,1%), gastrointestinais (52,3%), neurológicas (36,3%) e cardiovasculares (35,3%). Os principais desencadeantes foram: alimentos (43,0%), medicamentos (26,2%), himenópteros (21,6%) e látex (2,5%); os alimentos entre crianças (leite, ovo, amendoim/castanhas), e os fármacos (anti-inflamatórios e antibióticos) entre os adultos. Quanto ao tratamento, 61,1% recebeu adrenalina (52,7% por profissional e 8,4% via autoinjeter de adrenalina - AIA). Uma adolescente (12 anos) faleceu após picada de abelha. A maioria recebeu plano escrito de emergência (78,1%) e foi ensinada a usar o AIA (70%). **Conclusão:** Os alimentos foram os desencadeantes mais comuns entre crianças/adolescentes, e os fármacos entre adultos brasileiros. A adrenalina continua sendo subutilizada, reforçando a necessidade de maior disseminação do tratamento adequado da anafilaxia.

Descritores: Anafilaxia, hipersensibilidade alimentar, hipersensibilidade a drogas, hipersensibilidade a veneno, epinefrina.

Introduction

Anaphylaxis is defined a severe multisystemic allergic reaction of acute onset and potentially fatal.¹⁻³ Clinically, some or all of the following signs and symptoms may be present: urticaria, angioedema, respiratory and gastrointestinal involvement, and/or arterial hypotension.¹⁻⁴ The occurrence of two or more of these symptoms immediately after exposure to a likely allergen alerts to the diagnosis and the need for immediate treatment.^{1,3}

The incidence of anaphylaxis has been increasing in the last years, although there are few data on its epidemiology in Brazil. In most cases, literature is limited to studies with small population groups, with variable results depending on diagnostic criteria to define cases, study site, population assessed, study duration, among others.⁵⁻⁹

Registries have been a widely used tool in the study of diseases with a low prevalence, such as anaphylaxis.^{4,6,10-20} They allow for gathering and documenting, in an active and standardized manner, patients' data on predefined questions on clinical manifestations, treatment, and evolution. Registries also allows for assessing the efficacy in the clinical and laboratory medical care routine, in addition to the monitoring of patient safety as well as economic evaluation and minimum quantity (therapeutic) research required for disease control.¹⁷ In order to obtain more representative data on a given disease and to have a broader perspective about it, records are multicenter and/or multinational.^{6,10-20}

The Brazilian Anaphylaxis Registry of the Brazilian Association of Allergy and Immunology (*Registro Brasileiro de Anafilaxia da Associação Brasileira de Alergia e Imunologia*, RBA-ASBAI)²⁰ was developed based on the Portuguese Registry of Anaphylaxis and Adverse Reactions of the Portuguese Society of Allergy and Clinical Immunology (*Registro Português de Anafilaxia e Reações Adversas da Sociedade Portuguesa de Alergia e Imunologia Clínica*, RPARA-SPAIC)¹⁰, with the purpose of collecting national health data that allow us to gain a broader knowledge on the profile of Brazilian individuals affected by anaphylaxis. These data will be essential for physicians who treat these patients, as well as public power and society, to understand the importance of this problem, based on greater knowledge about the matter.

Method

This is an observational cross-sectional study aimed at assessing the characteristics of anaphylaxis in Brazilian individuals, using the RBA-SBAI, which is a national anaphylaxis registry that is completed online by the attending physician of a patient with a history of anaphylaxis.²¹ This questionnaire contains sociodemographic data, suspected triggers, clinical manifestations, treatment provided during the reaction, diagnostic workup, and post-reaction counseling.

The study was approved by the Research Ethics Committee (REC) of Instituto Pensi (No. 5.145.239).

In December 2021, this REC waived for mandatory signing of informed consent and assent free forms (ICF and IAF, respectively) for the inclusion of cases in the RBA-ASBAI.

Statistical analysis was performed by non-parametric tests, using the Jamovi® software (version 2.3). Categorical variables were described by frequency distribution, and continuous ones by mean and standard deviation (SD). P-values below 0.05 were considered statistically significant. The analysis included registries made from 06/28/2021 to 04/15/2023.

Results

Data from 237 patients were assessed, with a predominance of the female sex (131; 55.3%). Patients from 17 out of the 27 Brazilian states were included; state distribution ranged from 0.4% to 25.8% of the overall sample, with most patients coming from Southern and Southeastern states: São Paulo (25.8%), Paraná (19.4%), and Rio de Janeiro (15.6%). Patients were categorized as follows: 99 children/adolescents (< 18 years); 127 adults (18-64 years), and 11 older adults (65-77 years). There was a predominance of men among children and adolescents (55.5%; $p = 0.005$), and of women among adults (64.5%; $p = 0.002$). Overall median age was 22 years, and mean age was 25.6 (SD \pm 20.8) years (minimum < 1 year and maximum = 77). For the female sex, mean age was 27.8 (SD \pm 20) years and median was 29 years, while for the male sex, these values were 22.9 (SD \pm 21.5) years and 16 years, respectively. For 97/237 (39.2%) patients, the episode included in the RBA-ASBAI was the first one and, for 61/237 (25.8%) patients, it was the third one or more.

Household was the most frequent place of occurrence of the reaction (111/237; 46.8%), followed by hospital or health unit (37/237; 15.6%), park/field (27/237; 11.4%), restaurant (19/237; 8.0%), public space (16/237; 6.8%), and workplace (10/237; 4.0%). Nearly 95% of patients received some type of treatment, 68.4% (162/237) at an urgent service, 18.6% (44/237) at the place of occurrence of the reaction, 4.6% (11/237) at an intensive care unit, 3.4% (8/237) at an outpatient service, 3% (7/237) at an in-hospital ward, and 2.1% (5/237) at another place.

Symptoms occurred within the first 10 minutes after exposure to the allergen in 38.8% of the patients; from 10 to 30 minutes in 44.7%; from 31 to 59 minutes

in 7.2%; and after 1 hour in 7.1%. Biphasic reaction was observed in 10 patients (4.2%). There was predominance of cutaneous manifestations (92.8%), followed by respiratory (70.1%), gastrointestinal (52.3%), neurological (36.3%), and cardiovascular (35.3%) manifestations (Table 1). Urticaria was the most frequent cutaneous manifestation, with no differences regarding age, whereas angioedema predominated among individuals aged 65 years or older (Table 1). Respiratory manifestations predominated among those younger than 65 years, the most frequent of which was dyspnea, with no differences regarding age (Table 1). Rhinitis predominated among those younger than 18 years (Table 1). Gastrointestinal manifestations occurred similarly in the three age groups, and neurological manifestations were frequent among individuals aged from 18 to 64 years (Table 1). Hypotension was more frequent among older patients (Table 1).

For 133/137 (97.0%) patients who have had a previous episode, the previous one was more severe. Of these 133 patients, 55 were children, 71 were adults, and 7 were older adults (with no statistical difference among age groups). Only one 12-year old girl had a fatal outcome due to bee sting, a previously known allergen, because she was not treated with epinephrine.

Among the triggers, the most common were: foods (43.0%), drugs (26.2%), *Hymenoptera* sting (21.6%), and latex (2.5%) (Table 2). Foods predominated among patients younger than 18 years (27.4%), with cow's milk, egg, peanuts, and tree nuts being the most common allergens in this group, and seafood and wheat among individuals aged from 19 to 64 years (Table 2). Drug reactions predominated among adults (nonsteroidal anti-inflammatory drugs [NSAIDs], antibiotics, and latex) (Table 2). An analysis of variance (ANOVA) was conducted to investigate the differences for the "food" and "drug" triggers among the three different age groups: children, adults, and older adults. Results for ANOVA revealed significant differences in the "food" ($F = 7.3$; $p < 0.001$) and "drug" ($F = 3.62$; $p < 0.001$) variables among the age groups. In relation to insects, there was predominance of adults (ant, wasp, and bee), followed by children (ant, bee). For 78.9% of patients, there was no cofactor associated with the condition, whereas 6.3% appointed exercise, 5.4% drugs, 1.6% alcohol, and 1.6% stress as cofactors.

In relation to the treatment received, it was observed that 61.1% of patients received epinephrine (52.7%

Table 1

Clinical manifestations presented by patients included in the Brazilian Anaphylaxis Registry of the Brazilian Association of Allergy and Immunology during their most recent anaphylaxis episode, according to age group (% in relation to the number of individuals affected in each age group)

Clinical manifestations	Age group (years)			Total 237 (%)
	< 1 to 18 99 (%)	19 to 64 127 (%)	≥ 65 11 (%)	
Cutaneous	95 (96.0)	114 (89.8)	11 (100)	220 (92.8)
Urticaria	67 (67.7)	79 (62.2)	7 (63.6)	153 (64.6)
Angioedema	65 (65.6)	70 (55.1)	2 (18.2)	137 (57.8)
Generalized pruritus	37 (37.4)	59 (46.5)	7 (63.6)	103 (43.5)
Generalized erythema	26 (26.3)	32 (25.2)	4 (36.4)	62 (26.2)
Respiratory	69 (69.7)	94 (74.0)	5 (45.5)	168 (70.1)
Rhinitis	22 (22.2)	16 (12.6)	0	38 (16.0)
Oppression sensation in the throat	13 (13.1)	33 (26.0)	1 (9.1)	47 (19.8)
Stridor	2 (2.0)	10 (7.9)	0	12 (5.1)
Laryngeal cough	19 (19.2)	18 (14.2)	0	37 (15.6)
Dysphonia	10 (10.1)	16 (12.6)	0	26 (11.0)
Dyspnea	29 (29.3)	38 (29.9)	4 (36.4)	71 (30.0)
Mild bronchospasm	16 (16.2)	12 (9.4)	1 (9.1)	29 (12.2)
Moderate bronchospasm	12 (12.1)	11 (8.7)	0	23 (9.7)
Hypoxemia (SatO ₂ < 92%)	5 (5.0)	19 (15.0)	1 (9.1)	25 (10.5)
Respiratory arrest	0	2 (1.6)	0	2 (0.8)
Gastrointestinal	52 (52.5)	67 (52.8)	5 (45.5)	124 (52.3)
Edema labial	15 (15.2)	30 (23.6)	2 (18.2)	47 (19.8)
Oropharyngeal pruritus	5 (5.1)	25 (19.7)	0	30 (12.7)
Oppression sensation in the oropharynx	7 (7.1)	33 (26.0)	3 (27.3)	43 (18.1)
Nausea	10 (10.1)	16 (12.6)	0	26 (11.0)
Recurrent vomiting	23 (23.2)	13 (10.2)	0	36 (15.2)
Mild abdominal pain	6 (6.1)	8 (6.3)	0	14 (5.9)
Intense abdominal pain	2 (2.0)	5 (3.9)	2 (18.2)	9 (3.8)
Diarrhea	12 (12.1)	10 (7.9)	1 (9.1)	23 (9.7)
Loss of sphincter control	0	4 (3.1)	0	4 (1.7)
Neurological	28 (28.3)	54 (42.5)	4 (36.4)	86 (36.3)
Anxiety	6 (6.1)	20 (15.7)	0	26 (11.0)
Altered level of activity	10 (10.1)	10 (7.9)	0	20 (8.4)
Sensation of lipothimia	11 (11.1)	20 (15.7)	1 (9.1)	32 (13.5)
Confusion	0	9 (7.1)	0	9 (3.8)
Loss of consciousness	8 (8.1)	23 (18.1)	4 (36.4)	35 (14.8)
Cardiovascular	18 (18.2)	57 (44.9)	8 (72.7)	83 (35.0)
Tachycardia	7 (7.1)	24 (18.9)	1 (9.1)	32 (13.5)
Severe bradycardia	0	1 (0.8)	0	1 (0.4)
Dysrhythmia	0	0	0	0
Shock	0	7 (5.5)	1 (9.1)	8 (3.4)
Hypotension	13 (13.1)	35 (27.6)	8 (72.7)	56 (23.6)
Heart arrest	0	2 (1.6)	1 (9.1)	3 (1.3)

Table 2

Agents appointed as responsible for anaphylaxis in patients included in the Brazilian Anaphylaxis Registry of the Brazilian Association of Allergy and Immunology, according to age group in relation to the total sample

Triggering agent	Age group (years)			Total 237 (%)
	< 1 to 18 99 (%)	19 to 64 127 (%)	≥ 65 11 (%)	
Foods				
Cow's milk	32 (13.5)	0	0	32 (13.5)
Egg	13 (5.5)	2 (0.8)	0	15 (6.3)
Peanuts	6 (2.5)	0	0	6 (2.5)
Wheat	4 (1.7)	5 (2.1)	1 (0.4)	10 (4.2)
Nuts	2 (0.8)	0	0	2 (0.8)
Seafood	1 (0.4)	15 (6.3)	0	16 (6.8)
Fish	1 (0.4)	0	0	1 (0.4)
Kiwi	0	1 (0.4)	0	1 (0.4)
Other	6 (2.5)	11 (4.6)	0	17 (7.2)
Total	65 (27.4)	36 (15.2)	1 (0.4)	102 (43.0)
Drugs				
NSAIDs	1 (0.4)	20 (8.4)	1 (0.4)	22 (9.2)
Antibiotics	1 (0.4)	7 (2.9)	2 (0.8)	10 (4.2)
Biological agents	0	1 (0.4)	0	1 (0.4)
Anesthetics	0	1 (0.4)	0	1 (0.4)
Corticosteroids	0	1 (0.4)	0	1 (0.4)
Proton pump inhibitors	0	1 (0.4)	0	1 (0.4)
Contrast media	0	1 (0.4)	1 (0.4)	2 (0.8)
Muscle relaxant	0	1 (0.4)	0	1 (0.4)
Vaccine	0	1 (0.4)	0	1 (0.4)
Latex	1 (0.4)	4 (1.7)	1 (0.4)	6 (2.5)
Other	2 (0.8)	12 (5.1)	2 (0.8)	16 (6.7)
Total	5 (2.1)	50 (21.1)	7 (2.9)	62 (26.2)
Insects				
Ant	11 (4.6)	9 (3.8)	0	20 (8.4)
Bee	4 (1.7)	7 (2.9)	2 (0.8)	13 (5.5)
<i>Polistes spp. wasp</i>	2 (0.8)	8 (3.4)	0	10 (4.2)
<i>Vespula spp. wasp</i>	2 (0.8)	1 (0.4)	0	3 (1.3)
Other	0	5 (2.1)	0	5 (2.1)
Total	19 (8.0)	30 (12.7)	2 (0.8)	51 (21.5)
Outro				
Exercise	5 (2.1)	9 (3.8)	1 (0.4)	15 (6.3)
Cold	0	1 (0.4)	0	1 (0.4)
Total	5 (2.1)	10 (4.2)	1 (0.4)	16 (6.7)

(%) = percent of the total.

administered by a professional, and 8.4% via the anaphylaxis emergency kit). Only 25 patients carried the kit. The use of epinephrine in the emergency event was greater in adults than in children (58.3% vs 43.4%, $p < 0.05$), respectively. Antihistamines were used by 87.3% of patients, corticosteroids by 83.1%, bronchodilator by 27.4%, oxygen inhalation therapy by 29.5%, and volume replacement therapy by 30.8%. Ten patients were intubated (9 adults/1 older adult), who more frequently had a history of a more severe previous episode, and eight were resuscitated (6 adults/2 older adults), all of whom had a history of a more severe previous episode ($p = 0.039$).

With regard to patients' workup, it bears highlighting that only 24 (10.1%) underwent serum tryptase testing, which showed high levels in two; 149 underwent other complementary tests with the following frequency: specific serum IGE testing (101/149; 67.7%), skin test (62/149; 41.6%), and/or provocation test (13/149; 8.7%). Clinical history was highly suggestive in nine patients.

A large number of patients had already been referred to a specialist (42.6%) or was referred to after the anaphylaxis episode (50.2%). Epinephrine autoinjector (EAI) was prescribed to 68.8% of patients. With regard to counseling, it was observed that most patients were taught how to use the EAI (70%) and about the trigger (95.8%), prevention strategies (96.2%), and post-reaction practices (97%). The majority of patients received a written emergency plan (78.1%), but a minority received an anaphylaxis alert bracelet or medal (20.7%). In relation to immunotherapy, 30% of patients were advised to receive it.

Discussion

This study reported the first 237 patients who presented anaphylaxis and whose data were included in the RBA-ASBAI by their allergologist physicians.

Since anaphylaxis is a very severe and potentially fatal allergic reaction, it is important to understand its clinical evolution, its triggering agents, and the therapeutic approach adopted, in order to establish guidelines that allow for providing these patients with better care.

Similar to findings observed by other researchers who analyzed data from different sources (population samples, national or international registries, among others), cutaneous manifestations, especially

urticaria and angioedema, predominated.⁵⁻¹⁹ It bears emphasizing that, although urticaria is one of the items composing several diagnostic criteria for anaphylaxis, some patients may manifest it in the absence of cutaneous symptoms.^{1,3}

With regard to etiological agents, an important relationship was found according to patients' age, with foods predominating among younger patients, and drugs among the older ones, which corroborates findings from other registries.^{5,19} Such fact may be justified by the life stage when individuals are exposed to the allergen. Foods that are introduced early in life, such as milk and egg, are capable of inducing reaction already early in life, whereas seafood, whose food introduction occurs lately, triggered reactions at more advanced stages of life. The same can be said for drugs. It is worth highlighting that NSAIDs stand out as the main cause of drug-induced anaphylaxis in adults, as also noted by Jares et al. in Latin America.¹⁹

Concerning *Hymenoptera* venoms, it is important to bear in mind some aspects related to their exposure at different ages. Among adults, professional exposure (bees) predominates, while children and adolescents are exposed during leisure time (ant, bee). Other studies also showed ants as a relevant trigger in the pediatric population¹⁹.

With regard to the place of occurrence of the reaction, most episodes occurred at the patient's own house. This may be explained by the higher prevalence of food reactions in our sample and highlights the importance of having the EAI available and of providing proper counselling after the first reaction.

Although the treatment of choice at the acute phase of anaphylaxis was epinephrine, only 61.1% of patients in the study received it, applied mostly by a healthcare professional, less often among children and adolescents, and only 13.7% of patients used the EAI. What would justify this difference? Difficulty in establishing the diagnosis of anaphylaxis in individuals younger than 19 years? Less information by physicians who treat children at the emergency room? Less severe cases among the youngest?

Despite dissemination of recent knowledge and life support training currently received by most physicians, prescription of epinephrine, either intramuscular or subcutaneous, remains low, as opposed to the high prescription of antihistamine agents and corticosteroids.

A noteworthy finding is the fact that patients with previous history of severe episodes and need for

resuscitation were the ones who presented the most severe forms of anaphylaxis, requiring intubation and admission to the intensive care unit, all of whom were older than 19 years.

Serum tryptase testing has been one of the recommended biomarkers for anaphylaxis diagnosis and follow-up. Several factors interfere with its levels, especially at the time of collection in relation to the duration of the episode, which may justify the low incidence of positive results for this test in the present sample.

Specialized follow-up of these patients is very important to allow for identifying the etiological agent, in addition to instructing the patient with regard to the disease and its warning signs and to providing a written plan in case of emergency and, if possible, use of EAI. Fortunately, most registered patients received appropriate guidance on emergency plan and use of EAI.

Our study has limitations, because it was conducted by allergists only, with a non-random population sample, with a probable selection bias. Therefore, results cannot be generalized to the entire Brazilian population. Another weakness is recall bias, since the questionnaires were completed based on patients' reports. Despite this, it is worth highlighting the inadequate approach to which these patients were submitted. Conversely, there are some positive aspects, such as the nationwide coverage of the study and the fact that it included individuals with different dietary habits and environmental exposures, in addition to the use of a standardized questionnaire that was completed by trained professionals in recognizing anaphylaxis.

To conclude, analysis of the first patients with anaphylaxis included in the RBA-ASBAI points the need for greater awareness of cases of anaphylaxis and a more comprehensive education for lay people and other professionals, especially to prevent new episodes and provide proper treatment in case of recurrence.

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