

Anaphylaxis during the first year of life of infants with cow's milk protein allergy

Anafilaxia durante o primeiro ano de vida em pacientes com alergia à proteína do leite de vaca

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ABSTRACT

Objective: To describe the early manifestations of anaphylaxis in infants with cow's milk protein allergy (CMPA) and the therapeutic approach. **Method:** In this cross-sectional observational study, we retrospectively reviewed the medical records of patients with CMPA treated at the Institute for Children and Adolescents of Hospital das Clínicas, University of São Paulo Medical School, from 1990 to 2015. Patients who developed allergic symptoms during the first year of life and had a diagnosis of anaphylaxis were compared with allergic patients without anaphylaxis triggered by cow's milk. Patients were characterized according to epidemiological features, type of symptoms, and treatment received. Data were analyzed using GraphPad software. Associations between categories were assessed by Fisher's exact test, and groups were compared by the Mann-Whitney test. Results with $p < 0.05$ were considered statistically significant. **Results:** Of 120 infants evaluated (68 male: 52 female), 85 (70.83%) met the World Allergy Organization criteria for anaphylaxis. Most infants had cutaneous manifestations of immunoglobulin E (IgE)-mediated allergy ($n=102$, 85%). In those with a diagnosis of anaphylaxis, the main manifestations were urticaria ($n=39$, 45.8%), vomiting ($n=36$, 42.3%), and dyspnea ($n=19$, 22.3%). Anaphylaxis recurred in 41 patients (34.16%). Epinephrine (45%) and antihistamines (63.3%) were the most used drugs. Six patients (7%) with a diagnosis of anaphylaxis received no treatment. **Conclusion:** Anaphylaxis during the first year of life showed clinical features similar to those of older pediatric patients, but the rates of episode recurrence and undertreatment are still high. More education strategies need to be developed.

Keywords: Anaphylaxis, milk hypersensitivity, food hypersensitivity.

RESUMO

Objetivo: Descrever as manifestações de anafilaxia precoce em lactentes com alergia à proteína do leite de vaca (APLV) e descrever as condutas terapêuticas utilizadas. **Método:** Estudo observacional transversal retrospectivo que analisou pacientes com APLV atendidos no Instituto da Criança e do Adolescente do Hospital das Clínicas da FMUSP, entre 1990-2015, que apresentaram sintomas de alergia no primeiro ano de vida, com diagnóstico de anafilaxia, comparados a pacientes alérgicos sem anafilaxia desencadeada por ingestão de leite de vaca. Os pacientes foram caracterizados de maneira epidemiológica, tipo de sintoma apresentado e tratamento realizado. Os dados foram analisados no programa estatístico GraphPad Software Inc. Para avaliar a associação entre categorias, foi utilizado o Teste Exato de Fisher, e para comparações entre grupos, o Teste de Mann Whitney. Os resultados de $p < 0,05$ foram considerados significativos. **Resultados:** De um total de 120 crianças avaliadas (68 M:52 F), 85 (70,83%) lactentes preencheram os critérios da *World Allergy Organization* (WAO) para anafilaxia. As manifestações de alergia IgE mediada foram prioritariamente cutâneas [102 (85%)]. Nos pacientes com diagnóstico de anafilaxia, as principais manifestações foram urticária [39 (45,8%)], vômito [36 (42,3%)] e dispneia [19 (22,3%)]. A recorrência do episódio de anafilaxia ocorreu em 41 (34,16%) pacientes. A adrenalina (45%) e o anti-histamínico (63,3%) foram os medicamentos mais utilizados. Observa-se também que 6 (7%) pacientes com diagnóstico de anafilaxia não receberam nenhum tratamento. **Conclusão:** Anafilaxia no primeiro ano de idade apresenta quadro clínico semelhante aos pacientes mais velhos, mas ainda há elevada taxa de recorrência de episódios e subtratamento. Mais estratégias de educação precisam ser desenvolvidas.

Descritores: Anafilaxia, hipersensibilidade ao leite, hipersensibilidade alimentar.

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Introduction

Food allergy is a major public health concern, affecting at least 1-2% of children and adults.^{1,2} It is characterized by an adverse reaction to food that compromises the immune system involving IgE-mediated reactions, cell-mediated mechanisms (non-IgE mediated), or both (mixed mechanisms), as in eosinophilic esophagitis or atopic dermatitis.² In IgE-mediated reactions, symptoms occur within two hours of ingestion of the food, and histamine release is the main result of IgE action. Patients with IgE-mediated allergy have symptoms in various systems, which differs from non-IgE-mediated allergies, where gastrointestinal symptoms predominate. Urticaria, angioedema, vomiting, and bronchospasm are some of the symptoms reported by patients with IgE-mediated allergy, but anaphylaxis is the most feared manifestation.²

Anaphylaxis is an acute systemic or generalized life-threatening event. Several systems may be involved, but it is vascular instability or respiratory compromise that confer greater severity to the anaphylactic reaction.^{2,3} The increasing prevalence of allergic diseases has also resulted in an increase in the records of anaphylaxis.⁴

Foods are important causes of severe reaction triggers in adults, but even more so in children.⁵ In American studies, peanuts and tree nuts are the main causes of anaphylaxis, but milk ranks third.⁵ In Brazil, milk is the major food allergen, and although there are no prevalence studies on food allergy, two national studies involving presumed prevalence or office-based surveys confirm this premise.^{6,7} A national study found cow's milk allergy in children to be more prevalent by non-IgE mechanism, but this is a result conflicting with the literature, so this diagnostic hypothesis should be considered mainly according to the patient's clinical condition.^{8,9}

It is known that patients with CMPA present symptoms early, mostly in the first year of life, and in this setting, the identification of anaphylaxis can be more difficult, which may impair the outcome. It is known that early recognition of the disease is a crucial factor for initiating the therapeutic approach, which includes the administration of intramuscular adrenaline, an important measure to minimize the risk of death in these patients. There is a significant shortage of studies evaluating this particular age group, especially if we consider Latin America.¹⁰ It is important to recognize the characteristics of

anaphylaxis in the first year of life, the symptoms presented, and the evaluation of the therapy applied. In this context, we proposed this study, whose aim was to describe the manifestations of anaphylaxis in the first year of life in infants with CMPA and to characterize this population by comparing them to patients with the same allergy who did not present with anaphylaxis. A secondary objective was to also describe the therapeutic approaches to anaphylaxis in this age group.

Method

This was a retrospective cross-sectional observational study that analyzed the records diagnosed with CMPA that started their symptoms in the first year of life seen at the Child Institute (Instituto da Criança) at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (ICR-HC/FMUSP), from 1990 to 2015. This study was approved by the Research Ethics Committee of the Universidade Anhembi Morumbi under number 46370315.6.0000.5492.

Study population

We conducted a retrospective study that included data catalogued in the digital archive of the ICR-HC/FMUSP of patients who presented the following inclusion criteria:

- onset of symptoms of IgE-mediated CMPA before one year of age;
- diagnosis confirmed by suggestive clinical history associated with positive specific IgE to CM and/or fractions (specific serum IgE ≥ 0.35 kUA/L or positive prick test ≥ 3 mm, considered negative control 0) and clinical reproducibility evidenced on oral provocation test (OPT) with pure CM or Clinical history of anaphylaxis in the past 12 months after exposure to CM, associated with the presence of specific IgE to CM and/or fractions, even without performing OPT.

Patients whose data on the medical records were insufficient for analysis were excluded.

The data collected allowed the epidemiological and clinical characterization of the population using a protocol that includes a description of sex, date of symptom onset, presence of atopic diseases, diagnosis of anaphylaxis, description of manifested symptoms, affected systems, treatment introduced, and recurrence of the anaphylactic condition. The

patients were separated into two groups: those who presented characteristic symptoms of anaphylaxis and those who did not.

Patient manifestations were named anaphylactic when they met any of the three criteria proposed by the World Allergy Organization for diagnosing anaphylaxis (WAO - 2011).¹¹

The data were analyzed using GraphPad Prism version 8.0, available online at the website <http://www.graphpad.com/quickcalcs/index.com>. Numerical variables were described as mean, standard deviation, and 95% confidence interval (95%CI), and categorical variables as percentages or proportions. Continuous variables were expressed as median with their minimum and maximum values.

The Chi-square or Fisher's Exact tests were used to assess the association between categories, and comparison between groups was performed by either the Mann-Whitney or Kruskal-Wallis Test according to the number of groups. Standard error, 95% confidence interval, and statistical significance were reported. Significance was set at $p < 5\%$.

Results

We reviewed 120 medical records of patients who presented with symptoms of cow's milk protein allergy before one year of age. Among these infants, 52 (43.5%) were girls, and 68 (56.7%), boys. By carefully evaluating the diagnosis of the 120 patients,

85 (70.83%) met the criteria for anaphylaxis when analyzing the symptoms presented in the first episode of CMPA, while 35 (29.17%) did not meet the criteria. Both groups were named with acronyms for ease of mention; the group diagnosed with anaphylaxis was named "ANA" and the undiagnosed group "N-ANA." Although this study had the limitations inherent in a retrospective study, it was noteworthy that all symptoms reported by parents and the diagnoses of anaphylaxis were reviewed according to the proposed criteria.

The clinical and epidemiological characteristics are presented in Table 1. No differences were observed regarding sex and age of symptom onset (Fisher's Exact Test). The involvement by symptom system was primarily cutaneous, affecting 102 (85%) infants, followed by gastrointestinal symptoms in 58 (48.3%), respiratory symptoms in 38 (31.6%), and cardiovascular/systemic symptoms in 13 (10.8%) (Table 1).

In patients diagnosed with anaphylaxis, the main manifestations were urticaria [39 (45.8%)], vomiting [36 (42.3%)], and dyspnea [19 (22.3%)]. In patients who did not have a diagnosis of anaphylaxis, the main manifestations were urticaria [7 (20%)], perioral hyperemia [7 (20%)], and vomiting [9 (25.7%)] (Table 1).

Recurrence of anaphylaxis episodes occurred in 41 (34.16%) patients, who were known to have been previously diagnosed with anaphylaxis. Evaluation of

Table 1

Treatment used in the anaphylactic episode in children under one year of age compared with treatment performed in patients who did not present anaphylaxis

Treatment of first episode referred to as anaphylactic	Total (n = 120) n (%)	ANA (n = 85) n (%)	N-ANA (n = 35) n (%)
Adrenaline	54 / 45	52 / 61.1	2 / 5.7
Antihistamine	76 / 63.3	44 / 51.7	32 / 91.4
Corticoid	44 / 36.6	20 / 23.5	24 / 68.5
None	9 / 7.5	6 / 7	3 / 8.6
Inhaled beta-2	4 / 3.3	4 / 4.7	–

anaphylaxis recurrence was performed only in patients diagnosed with anaphylaxis under one year old.

Among the patients who had not been previously diagnosed with anaphylaxis, 9 had their first manifestation after the first year of life, and it was not possible to precisely define the number of episodes that occurred by analysis of the medical records, only their existence (Table 1).

Regarding associated atopic diseases throughout the follow-up, rhinitis was the most prevalent, with 50 (41.7%) patients diagnosed, followed by asthma, with 48 (40%), and atopic dermatitis, with 25 (20.8%), and there were no significant differences between the two groups (Table 1).

Regarding the treatment of anaphylaxis (Table 2), considering the entire sample ($n = 120$), we observed that adrenaline (45%) and antihistamine (63.3%) were the most prevalent drugs. In patients diagnosed with anaphylaxis, this pattern was repeated [adrenaline (61.1%) and antihistamine (51.7%)], and in patients without a diagnosis of anaphylaxis, the most prevalent treatments were antihistamine (91.4%) and corticoid (68.5%). It was also observed that six (7%) patients diagnosed with anaphylaxis did not receive any treatment. In contrast, two (5.7%) patients without a diagnosis of anaphylaxis received adrenaline.

Fisher's Exact Test was used to compare ANA and N-ANA pairs for respiratory ($p = 0.6832$) and gastrointestinal ($p = 0.1098$) manifestations, with no significant p -value. On the other hand, when assessing skin ($p = 0.01$) and cardiovascular ($p = 0.003$) manifestations there was statistical significance.

The recurrence rate of anaphylaxis was high, 41/120 patients had anaphylaxis and recurred later. Nine patients did not have anaphylaxis before 1 year and after this age presented cow's milk anaphylaxis. There was no correlation between early anaphylaxis and recurrence of anaphylaxis ($p = 0.2928$). A high prevalence of other, unrelated to the presence of anaphylaxis before the first year of life, was observed.

Discussion

The major contribution of this study was to better understand the manifestations of anaphylaxis in young infants, particularly in the first year of life. There are few studies in the literature that specifically evaluate children in this age group. It is known that foods are the main causes of anaphylaxis, and cow's milk proteins

are among the most frequent allergy triggers.^{11,12} The early onset of symptoms is one of the highlights of this study, with reports of symptoms such as erythematous plaques and vomiting as early as the first day of life. These manifestations reinforce the possibility of intrauterine sensitization and highlight the offer of polymeric formula in the nursery as a possible trigger of symptoms. The median onset of symptoms in IgE-mediated allergies was quite early (4 months), but there was no distinction in the age of symptom onset between anaphylactic and non-anaphylactic patients. A point for discussion and a limitation of this study is the non-uniformity in the amount of milk ingested by patients in the anaphylactic and non-anaphylactic groups. Since the intakes were casual, it is possible to speculate that patients with anaphylaxis may have ingested larger amounts or more allergenic preparations (unprocessed foods) than patients who did not have anaphylaxis in the first year of life, which is a possible confounding factor. Importantly, the reasons why certain patients with CMPA develop anaphylaxis and others do not are not fully understood. But factors such as fasting, the presence of infections, or the amount of food ingested may be relevant to the outcome of anaphylaxis, and these factors were not evaluated in this study.

Clinical manifestations of IgE-mediated food allergy occurred mainly on the skin in both groups, but significantly more frequently among the anaphylactic patients. The frequency of cutaneous manifestations in this group was similar to those described in the older populations. It is known that cutaneous manifestations are usually the most frequent, approximately 80%, in children diagnosed with anaphylaxis, regardless of the triggering agents.¹³⁻¹⁵ Right after the skin, the gastrointestinal system seems to be the most affected, affecting almost half of the patients. In this study, respiratory symptoms were much more frequent in patients with anaphylaxis, being described in isolation in a minority of cases. It is worth noting that isolated respiratory manifestations are even the least frequent among patients with IgE-mediated allergy, but they are not negligible. However, it is always worth noting that the respiratory symptoms associated with IgE-mediated food allergy occur about two hours after the administration of the food, and do not remain continuous, as do other causes of wheezing.¹³⁻¹⁵

In our study, there was no relationship between the occurrence of anaphylaxis and the development of other atopic diseases, especially atopic dermatitis. The association between atopic dermatitis and anaphylaxis

Table 2

Clinical-epidemiological characteristics of the 120 patients with CMPA manifestations in the first year of life (description of symptoms according to data in the medical chart)

Characteristics	Total N (%)	ANA (n = 85) N (%)	N-ANA (n = 35) N (%)	p
Sex				
Boys	68 (56.6)	47 (55.2)	21 (60)	0.689
Age at symptom onset median in days (min-max.)	120 (1-365)	120 (7-365)	120 (1-300)	

Manifestations of anaphylaxis in children under one year of age

Cardiovascular /systemic symptoms	13 (10.8)	13 (5.2)		NA
Hypotonia	7 (5.8)	7 (8.2)	–	–
Cyanosis	4 (3.3)	4 (4.7)	–	–
Loss of consciousness	1 (0.8)	1 (1.1)	–	–
Intense crying	1 (0.8)	–	1 (2.8)	–
Anaphylactic shock	1 (0.8)	1 (1.1)	–	–
Skin symptoms	102 (85)	78(91,7)	24 (68.5)	0.003
Urticaria	66 (55)	56 (65.8)	10 (2.8)	–
Angioedema	67 (56)	64 (75.2)	3 (0.08)	–
Perilabial hyperemia	11 (9.1)	4 (4.7)	7 (0.2)	–
Perioral papule + facial hyperemia	7 (5.8)	2 (2.3)	5 (0.1)	–
Erythroderma/Rash	7 (5.8)	6 (7)	1 (0.02)	–
Pruritus	5 (4.1)	4 (4.7)	1 (0.02)	–
Respiratory symptoms	38 (31.6)	33 (38.8)	5 (14.2)	0.6832
Dyspnea	21 (17.5)	19 (22.3)	2 (0.05)	–
Wheezing	13 (10.8)	12 (14.1)	1 (0.02)	–
Cough	6 (5)	5 (14.2)	1 (0.02)	–
Runny nose	1 (0.8)	1 (1.1)	–	–
Gastrointestinal symptoms	58 (48.3)	46 (54.1)	12 (34.2)	0.1098
Vomiting	45 (37.5)	36 (42.3)	9 (25.7)	–
Diarrhea	11 (9.1)	8 (9.4)	3 (8.5)	–
Colic	5 (4.1)	3 (3.5)	2 / (5.7)	–
Regurgitation	2 (1.6)	2 (2.3)	–	–

Other anaphylaxis episodes

Patients with anaphylaxis during the first year who presented other anaphylaxis episodes	41 (34.1)	41 (48.2)	NA	–
First anaphylaxis in > 1 year of age	9 (7.5)	NA	9 (25.7)	–

is a well-known risk factor, comprising about 58% of the cases analyzed in a multicenter study conducted in Italy.¹¹ However, the result of the present study allows us to argue that although anaphylaxis and atopic dermatitis are strongly correlated, the precocity of anaphylaxis below one year of age is not a greater risk factor. Another risk factor analyzed in this Italian study was sex, with boys being the most affected.¹¹ This is compatible with our sample, which showed more male patients, but this was not a risk factor for the development of anaphylaxis during the first year of life.

The recurrence of anaphylaxis was another point raised and studied in the present study, reaching a percentage of 34.1% in the general data. We believe that the number of patients included in this study was insufficient to show us a relationship between the previous episode of anaphylaxis and its recurrence; however, it is important to emphasize that the possibility of recurrence exists, as patients who had already been diagnosed with anaphylaxis recurred, showing the importance of guidance for parents in order to avoid recurrence.

The treatment performed during anaphylactic crises was also surveyed, showing inequality in the treatment of anaphylactic symptoms in one-year-olds or younger infants. It is noteworthy that patients with anaphylaxis did not receive proper treatment, but not only that, what is even more alarming is that there were patients who did not even receive any treatment, and fortunately there was no fatal outcome. This reflects the difficulty of physicians in diagnosing anaphylaxis and also a lack of knowledge when it comes to choosing the appropriate medication. All these factors can be further aggravated in children under one year old. The inexperience of parents, pediatricians in some emergency services, fear of using adrenaline, and difficulty in establishing the diagnosis are only some of the factors that can contribute to delayed medication, as also highlighted by Simons et al.¹⁵

The use of adrenaline as rescue therapy is widespread in other countries, and its use is recommended on a large scale. Since adrenaline is the medication with the best results in an anaphylactic reaction, its use, even in more than one dose, could be better recommended and known by the professionals who work in the first aid team.^{16,17} Intramuscular injection of adrenaline is the treatment of choice in anaphylaxis. Its plasma peak reaches high concentrations in a short period of time, bringing almost immediate effects to the patient.¹⁸

A study in Japan shows that pediatricians are poorly trained and unable to identify an ongoing anaphylactic condition, nor are they trained to properly treat pediatric patients in an anaphylactic crisis, and their deficiencies in management may result in failure to diagnose and prevent recurrences of anaphylaxis.¹⁹

Since the diagnosis in these patients can be quite difficult given the non-specificity of the symptoms, it is important to properly recognize the infants at risk, the triggering factors, the risk and recurrence factors present in the personal history, and the appropriate treatment.

There are several hypotheses to explain the growth of food allergy in infants, such as the use of antibiotic therapy by pregnant women during the perinatal period and prematurity. The use of antimicrobials would affect the fetal immune response by reducing intestinal tolerance cytokines, such as IL-10 and TGF- β ; in prematurity, the immaturity of the gastrointestinal barrier could be related to the breakdown of the intestinal barrier and lower evolution of tolerance.¹⁷ In our sample, it was not possible to collect these data on the perinatal period, and it is not possible to establish relationships.

Anaphylaxis in infants under one year of age is an event that needs to be more widely known, especially with the increasing prevalence of food allergies. Cow's milk stands out as the most frequent food in this age group. Although its manifestations resemble the symptoms in older age groups, there is a large number of children who do not receive appropriate treatment even in emergency services. Increased information and continuing education for family members and physicians in the emergency room can minimize the recurrence of symptoms and allow for more appropriate treatment.

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