

Anaphylaxis: aetiological diagnosis

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Background: Anaphylaxis is a generalised, immediate, potentially life-threatening reaction. **Methods:** We here report the clinical and etiological characteristics of 274 patients diagnosed of anaphylaxis between 1994 and 1995 at an Allergy Unit with a referral catchment population of 500,000. The patients' ages ranged between 6 months and 84 years (mean age, 34.4 years, median age 32 years); twenty-six of the patients (9.5%) were under 15 years in age. **Results:** The most frequent aetiology was represented by drugs (128 cases, 46.7%), followed by reactions to foodstuffs (62 cases, 22.6%), insect stings (38 cases, 13.9%), latex allergy (14 cases, 5.1%) and physical exertion in association to foodstuff ingestion (11 cases, 4%). In 16 cases (5.8%) the cause could not be ascertained (idiopathic anaphylaxis). The diagnosis was established by the clinical history in 21.2% of the cases. Positive skin tests were obtained in 74.8% of the cases, and specific IgE to the suspect allergen was detected in the sera of 44.2% of the patients. The clinical manifestations were cutaneous in 94.5% of the cases, respiratory in 66.1%, gastrointestinal in 28.8%, cardiovascular in 30.7% and neurological in 22.6%. Forty patients were treated with adrenaline at the time of the index episode, while 75 did not receive any form of drug treatment. After the allergy study, avoidance of the causative agent was recommended to all patients in whom an aetiological diagnosis had been established; self-injectable adrenaline was prescribed to 73 patients (26.6%), and various other measures were instituted in 23 cases. **Conclusions:** In the region of Navarre, drug ingestion is the most frequent cause of anaphylaxis, followed by food ingestion and, occasionally, by other agents and causes. Adrenaline is not used with the desirable and necessary frequency for the emergency management of anaphylaxis.

KEY WORDS: Anaphylaxis / Adrenaline / Diagnosis / Aetiology / Management.

Anafilaxia: diagnóstico etiológico

Fundamento: La anafilaxia es una reacción generalizada, de rápida instauración y que puede originar un cuadro clínico potencialmente amenazador para la vida. **Métodos:** Se evalúan las características clínicas y etiológicas de 274 pacientes diagnosticados de anafilaxia durante 1994 y 1995 en una Sección de Alergología que atiende una población de 500.000 habitantes. La edad de los pacientes osciló entre 6 meses y 84 años (media 34,4, mediana 32 años); 26 de ellos (9,5%) eran menores de 15 años. **Resultados:** La etiología más frecuente fue la medicamentosa (128 casos, 46,7%), seguida de la alimentaria (62 casos, 22,6%), las picaduras de insectos (38 casos, 13,9%), la sensibilización al látex (14 casos, 5,1%) y el ejercicio dependiente de alimentos (11 casos, 4%). En 16 pacientes (5,8%) no fue posible identificar la etiología (anafilaxia idiopática). La historia clínica fue el criterio diagnóstico en el 21,2% de los casos. En el 74,8% de los pacientes se obtuvieron pruebas cutáneas positivas, y en el 44,2% se detectó IgE específica para el alérgeno sospechado en suero. Los síntomas descritos fueron cutáneos (94,5%), respiratorios (66,1%), digestivos (28,8%), cardiocirculatorios (30,7%) y neurológicos (22,6%). En el momento del episodio, 40 pacientes recibieron tratamiento urgente con adrenalina y 75 no recibieron ningún tratamiento. Tras el estudio alergológico, en todos los casos en que se identificó el agente causal se recomendó la evitación del mismo; en 73 pacientes (26,6%) se prescribió adrenalina autoinyectable, y en 23 se aplicaron otras medidas. **Conclusiones:** En Navarra, los medicamentos son la causa más frecuente de anafilaxia, seguidos de los alimentos y, a más distancia, de otras sustancias. La adrenalina no se utiliza con la frecuencia necesaria y deseable como tratamiento urgente de la anafilaxia.

PALABRAS CLAVE: Anafilaxia / Adrenalina / Diagnóstico / Etiología / Tratamiento.

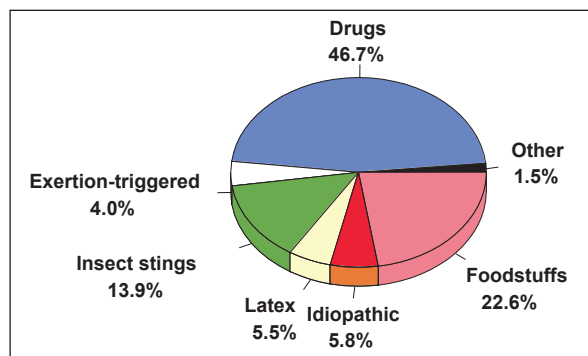


Fig. 1. Aetiology of anaphylaxis.

Anaphylaxis is a potentially life-threatening clinical syndrome characterised by its rapid development and its multisystemic clinical manifestations. Anaphylactoid reactions, which are clinically indistinguishable from anaphylaxis, can be differentiated from it because no IgE-mediated mechanism can be demonstrated¹.

There are many agents or circumstances which have been reported as triggering anaphylactic or anaphylactoid reactions: foodstuffs²⁻⁴, drugs⁵, insect stings⁶, latex allergy⁷ and physical exertion in association to foodstuffs⁸, among others. In a number of cases it has been impossible to identify the cause, and these cases have been labelled as idiopathic^{9,10}.

The present retrospective study assesses the characteristics of the patients diagnosed of anaphylaxis in the years 1994 and 1995 at an Allergology Section with a catchment population of 500,000 inhabitants. Particular attention has been given to the clinical features, the aetiological diagnosis and the therapeutic measures instituted both during the acute episode and after the allergy study had been completed.

PATIENTS AND METHODS

We have reviewed the clinical files of all the patients diagnosed of anaphylaxis, anaphylactic shock and anaphylactic reaction, according to the above definition, in the years 1994 and 1995; anaphylactoid reactions were excluded from the study. Individual filing cards were completed with the characteristics of each patient at the time of the allergy study and during the later evolution for the two years of the study.

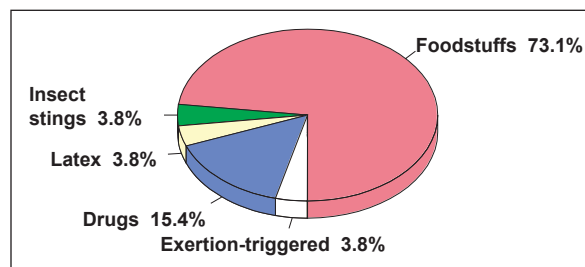


Fig. 2. Aetiology of anaphylaxis in the paediatric age group.

A detailed clinical history regarding the episode or episodes experienced was recorded for each one of the patients referred to the Allergology Section with a previous diagnosis of suspected anaphylaxis. On the basis of the clinical suspicion diagnosis derived from the anamnesis, a programmed allergy study was set up. This study included skin tests (modified prick tests or intradermal tests) according to previously described techniques¹¹ with the one or more suspected causative agents and with representatives from other clinically or taxonomically related allergenic groups considered to be individually opportune in each case (foodstuffs, drugs, latex, airborne allergens or other involved or related agents). Further studies were included whenever possible if they considered necessary for the differential and definitive diagnosis in each case (specific IgE antibodies to the presumably involved allergens, challenge tests with drugs or foodstuffs, prick-by-prick with some of the involved foodstuffs, serologic tests for *Echinococcus* disease, etc).

The χ^2 test was used for comparing the frequencies of the aetiological agents involved according to the patients' ages (adults and children).

RESULTS

The demographic data of the patients are summarised in Table I.

The clinical history was the single diagnostic criterion in 21.2% of the patients; in these cases, the cause-effect relationship was univocal and clear (drugs) and the manifestations of anaphylaxis had been very severe, so that the practice of additional tests was deemed not to be advisable in order to avoid possible risks to the patient.

Table I. Demographic characteristics of the patients studied

Number of cases	274
Age	
• Range (years)	0.5 - 84
• Below 15 years (%)	26 (9.5%)
Gender (%)	
• Males	49.3
• Females	50.7
Atopics (%)	25.2

Positive skin tests with the agent(s) suspected as cause of the reaction were obtained in 74.8% of the cases. In 44.2% of the cases, specific serum IgE antibodies to the causative agent(s) were detected.

The most frequent cause of anaphylaxis in this series (Fig. 1) were drugs (46.7% of the patients, $n = 128$); β -lactam antibiotics were the most frequently involved drug group (54.7% of the drug-induced cases), followed by pyrazolones (25.8%). Foodstuffs were the second cause in order of frequency (22.6%, $n = 62$); foremost among them were fruits (in the majority of the cases *Rosaceae*), nuts, seafoods and/or shellfish, legumes, milk, egg and fish. Insect venoms (13.9%, $n = 38$) represented the third most frequent cause.

Further causes of anaphylaxis were latex allergy (5.1%, $n = 14$), physical exertion in association with foodstuffs (4%, $n = 11$) and the group of "other causes" (1.8%, $n = 5$). No apparent cause could be detected (idiopathic anaphylaxis) in 5.8% of the cases ($n = 16$). One of the cases included in this last category was diagnosed, at a date beyond the studied period, as a case of anaphylaxis due to ingestion of *Anisakis*, a parasite of fish which has been recently described as a cause of this particular clinical picture¹².

Within the paediatric age group (Fig. 2), the most frequent cause were foodstuffs (73.1%, 19 out of the 26 cases); the foremost causative agents in this aetiological group were milk (5 cases), egg (4 cases), legumes (4 cases) and, with lesser frequency, seafoods/shellfish ($n = 2$), fruits ($n = 2$), nuts ($n = 1$) and meats ($n = 1$). A much less frequent cause of anaphylaxis in this group were drugs ($n = 4$, 15.4%); even less frequent, with only one case of each, were *Hymenoptera* venom, latex allergy, and exertion-induced anaphylaxis.

Table II. Therapy for anaphylaxis received by the patients during the acute episode and after the allergy study

	No. of cases (%)
Acute episode	
Adrenaline	40 (14.6)
Other	60 (21.9)
None	75 (27.4)
Unknown	99 (36.1)
After the allergy study	
Avoidance of the causative agent	258 (94.2)
Immunotherapy	30 (10.9)
Self-injectable adrenaline	73 (26.6)
Other	23 (8.4)

According to these data, foodstuff-induced anaphylaxis is much more frequent in children (73.1%) than in adults (17.3%) (O.R. 12.94, CI 4.78 - 38.27); inversely, the frequency of drug-induced anaphylaxis is much greater in the adult population (50%) than in the paediatric one (15.4%) (O.R. 5.50, CI 1.79 - 22.47).

The clinical manifestations of anaphylaxis showed the following distribution and frequencies: there were cutaneous or mucosal symptoms in 94.5% of the cases, 66.1% evidenced respiratory symptoms, cardiovascular signs and/or symptoms were recorded in 30.7% of the cases, 28.8% of the patients reported gastrointestinal symptoms, and in 22.6% of the cases neurological symptoms were recorded.

Only 14.6% of the patients received adrenaline in the management of the acute episode (Table II); in 27.4% of the cases no treatment at all was given.

After the allergy study was completed, avoidance of the causative agent could be recommended in 94.2% of the cases (all those in which an aetiological diagnosis was established); self-injectable adrenaline was prescribed to 26.6% of the patients, who received instructions regarding its use¹³, and specific immunotherapy was indicated in 30 patients (10.9% of all anaphylaxis cases) with *Hymenoptera* venom anaphylaxis¹⁴ (78.9% of all patients with insect sting anaphylaxis).

A reassessment of the particular case was not carried out in 46.7% of the patients within the study period, either because they had been definitively discharged, because the review and reassessment was performed at a later date, beyond the studied period, or because they did not return for consultation. Among the remainder of the patients, those in whom an aetiological diagnosis had been

achieved reported clinical improvement, defined as complete absence of further anaphylactic episodes or, when these had recurred, by a much lesser frequency and/or severity of the symptoms. The patients diagnosed of idiopathic anaphylaxis did not report any clinical improvement.

DISCUSSION

Anaphylaxis is the immunologically triggered clinical picture which requires the most urgent treatment because of its usually rapid instauration, rapid progression and extreme severity, which can lead to the death of the patient⁴. The rapidity of its development correlates with the severity of the clinical picture¹⁵. The cardiovascular and respiratory symptoms are the most important ones, and the ones that may cause death¹⁶. The complementary studies do not yield pathognomonic data with the exception of the determinations of serum tryptase¹⁷, a specific mast cell protein that is released in the course of their activation. However, as this determination requires time, it is not useful for the diagnosis of the acute episode at the time it occurs, but only, if it is found to be increased, for the later confirmation that the episode was actually one of anaphylactic reaction. In many cases, true anaphylactic episodes are diagnosed as mere allergic reactions, leading to an erroneous management and follow-up^{18,19}. Once a patient has experienced an episode suspected to have been an anaphylactic reaction, all possible and necessary efforts must be made in order to identify the causative/triggering agent²⁰. This enterprise is neither always simple nor easy^{21,23}, as avoidance of the causative agent is the main weapon available in order to prevent or avoid a new anaphylactic episode. Furthermore, reports have been published which show that the adequate study and management of anaphylaxis can significantly reduce the health care costs caused by repeated hospital (or emergency ward) admissions because of incorrect diagnoses and/or treatments¹⁰. In the future, many of the processes which are today labelled as idiopathic anaphylaxis may well be removed from that category, as a result of a more exhaustive questioning and study and of the development of new knowledge and techniques; a good example of this is the one case of (subsequently diagnosed) *Anisakis*-triggered anaphylaxis in the present series.

The lack of new consultations by the patients who were eventually discharged and by many of those who simply did not return ("lost to follow-up") suggests that they had a satisfactory evolution. In the case of the patients who, despite an aetiological diagnosis and attendant measures, did experience new albeit lesser episodes of anaphylaxis, this was due to inadvertent contacts with the identified aetiological agent (generally, episodes triggered by drugs or foodstuffs).

A frank improvement (97,9%) was observed in the patients who were subsequently followed in the allergy outpatient clinic; this improvement manifested itself in a complete disappearance or a reduction in frequency and severity of the anaphylaxis episodes after the allergy study.

In the region of Navarra, drugs represent the most frequent aetiology of anaphylaxis, followed by foodstuffs. In the age group below 15 years, however, the most frequent cause of anaphylaxis is the alimentary one, in agreement with other published studies²⁴. According to these data, patients under 15 years of age have a 12-fold risk of developing foodstuff-induced anaphylaxis as compared to adults.

Even though in the present series all the patients experienced a complete resolution of their anaphylaxis episodes, it is obvious that failures in the diagnosis, and hence in the recognition of the severity of the syndrome, would delay the institution of adequate therapeutic measures. According to our observations, adrenaline, even though it is the treatment of choice in anaphylaxis^{13,25-30} is but infrequently used in its emergency management. This entails an increased risk that the episode may have a fatal evolution²⁷. Because of the rapid progression of the clinical picture, therapeutic measures must be instituted immediately. These therapeutic measures can, although not in all cases, prevent progression²⁷. Once the allergy diagnosis has been established, the main therapeutic measure will be the avoidance of the causative agent; this can in some instances entail problems, particularly from the nutritional point of view (malnutrition, occult allergens in prefabricated foods, etc.), rendering a multidisciplinary approach to the problem (primary health care physicians, paediatricians, dieticians, allergy specialists) highly advisable.

Anaphylaxis is a severe clinical picture that occasionally remains undiagnosed. Treatment with adrenaline, though clearly indicated, is not

carried out with the desirable frequency. The aetiological diagnosis, which is very often possible and feasible, is fundamental for preventing the apparition of new episodes in a patient who has already experienced one.

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