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Original article

Anaphylaxis in northern Extremadura

Background: Antigenic exposure is different for each geographic area, as a consequence of the various allergens locally present and of the customs and habits (alimentary, occupational and drug-intake) of the population. **Methods:** We have carried out, over a period of two years, an observational, prospective and cross-sectional epidemiologic study (Plasencia 98-99) in which 1,450 consecutive patients of any age and coming from northern Extremadura (Spain) were included who had been seen at our Allergy Outpatient Clinic, in order to assess the incidence of the various allergic processes, their importance at the various ages and gender, and their aetiology. **Results:** The study population included 820 women (59.3%) and 630 males (40.7%). The mean age was 25.9 years. Anaphylaxis was diagnosed in 58 cases (4%). There was no gender predominance for this diagnosis; the mean age of the patients was 35.6 years and the peak incidence occurred in the 25 to 45 year age group. The cause of the anaphylaxis episode was drug intake in 36 patients (62%), the most frequently involved drug families being β -lactam antibiotics (amoxycillin 15.5%, penicillin G 15.5%) and pyrazolones (magnesium dipyrone 13.7%). Food intake was the cause in 14 cases (24.1%), the major single causative ones being honey (6.8%), lentils (6.8%), green beans (6.8%), peas (5.17%), haricot beans (5.17%), chickpeas (5.17%) and sunflower seeds (5.17%). Five cases (8.6%) were caused by *Hymenoptera* venom allergy [4 by bee (6.8%) and one by wasp stings (1.7%)]. No definite aetiology could be found in two cases (3.4%). One patient (1.7%) had exertion-induced anaphylaxis, and another one (1.7%) an episode of urticaria *a frigore* with systemic symptoms after bathing in cold water. **Conclusions:** Drug intake is the major cause of anaphylaxis in northern Extremadura with slightly over one-half of the cases, followed by food intake with about one-fourth. The three single allergens that caused the most reactions were amoxycillin, penicillin G and magnesium dipyrone.

Key words: Anaphylaxis. Epidemiology.

Anafilaxia en el norte de Extremadura

Fundamento: La exposición antigénica difiere en cada área geográfica y ello depende de los diversos alérgenos presentes en cada zona y de los hábitos (alimentarios, laborales, ingesta de fármacos) de la población. **Métodos:** Durante dos años se realizó un estudio epidemiológico (Plasencia 98-99) observacional, prospectivo y transversal, en el que se incluyeron 1.450 pacientes consecutivos, de cualquier edad, atendidos por primera vez en nuestra consulta de Alergología y procedentes del norte de Extremadura (España), con la finalidad de conocer la incidencia de los distintos procesos alérgicos, su importancia según la edad y el sexo y la etiología de los mismos. **Resultados:** Se estudiaron 820 mujeres (59,3%) y 630 varones

(40,7%). La edad media fue de 25,9 años. En 58 pacientes (4%) se diagnosticó anafilaxia. No hubo predilección por el sexo. La edad media fue de 35,6 años. La mayor incidencia ocurrió entre los 25 y los 45 años. En 36 pacientes (62%) fue debida a medicamentos, especialmente de las familias betalactámicos (amoxicilina 15,5%, penicilina G 15,5%) y pirazolonas (dipirona magnésica 13,7%). En 14 (24,1%) la causa fue un alimento (miel 6,8%, lenteja 6,8%, judía verde 6,8%, guisante 5,17%, alubia 5,17%, garbanzo 5,17%, pipas de girasol 5,17%). En 5 (8,6%) se debió a alergia a veneno de himenópteros, 4 por abeja (6,8%) y uno por avispa (1,7%). En 2 casos (3,4%) no se encontró ninguna etiología. Un paciente (1,7%) tuvo anafilaxia inducida por ejercicio y otro (1,7%) urticaria "a frígore" con síntomas sistémicos tras un baño en agua fría. **Conclusiones:** En el norte de Extremadura los fármacos son la principal causa de anafilaxia, en algo más de la mitad de los casos, seguido de los alimentos en la cuarta parte. Los tres antígenos que causaron más reacciones fueron amoxicilina, penicilina G y dipirona magnésica.

Palabras clave: Anafilaxia. Epidemiología.

Antigenic exposure is well known to differ in each geographic area, and this variability depends on the various airborne allergens and *Hymenoptera* present within each ecosystem and on the habits of the population regarding the types of foods ingested, the occupational activities or the drugs consumed either upon medical prescription or through self-medication. An assessment of the peculiarities of our own area of influence was the stimulus that induced us to carry out the first ever general epidemiologic study on allergic diseases in the northern area of Extremadura (Spain), which we called the "Plasencia 98-99 Study"; the results of this study regarding anaphylaxis are now presented.

Since the publication of the "Alergológica 92" study¹, Spanish allergologists have available an excellent reference with which to compare their own results, even though in this study such an important subject as anaphylaxis was not treated in a separate chapter.

MATERIAL AND METHODS

The Plasencia 98-99 Study was an observational, cross-sectional and prospective study for the assessment and

analysis of all the diagnoses established at our Allergy Clinic after a complete clinical evaluation of the patients. The study included 1,450 consecutive patients of all ages who were seen for the first time during the years 1998 and 1999 and who originated from the Plasencia, Coria and Navalmoral de la Mata Health Care Areas in northern Extremadura (Spain). Previously diagnosed cases were excluded. At the end of each patient's allergologic assessment, the following data were registered in a pre-established form: age, gender, clinical features, allergologic tests performed (both *in vitro* and *in vivo*), and final diagnosis. This information was then transferred to a digital database for analysis.

A diagnosis of anaphylaxis was established in those severe systemic reactions occurring with simultaneous or consecutive involvement of several organs or systems, with cutaneous (urticaria, angioedema, pruritus, ...), respiratory (bronchospasm, upper airway oedema, ...), gastrointestinal (vomiting, diarrhoea, abdominal pain, ...) and/or cardiovascular (hypotension, anaphylactic shock, ...) manifestations².

The painstaking anamnesis of everything that happened within the hour preceding the acute episode provided the fundamental aetiologic suspicion, and this was in many cases confirmed through positive skin tests and/or CAP results to the suspected allergen. Because of ethical reasons no patient was subjected to challenge tests, so that, in a number of cases of drug allergy, the final diagnosis was only a suspicion one.

The skin tests were carried out by the prick method according to the usual procedure³, with airborne allergen extracts from Alk-Abelló, S. A., Madrid, Spain, and food and foodstuff extracts from CBF Leti, S. A., Barcelona, Spain. The "prick-by-prick" technique with the fresh product was used in some cases when an allergenic extract was not commercially available. In the case of *Hymenoptera* venom allergy, commercial extracts from Alk-Abelló were used³. The tests were performed on the volar aspect of the forearm using lancets with a 1-mm point (Prick Lancet, Bayer, Leverkusen, Germany), with both positive and negative control tests (10 mg/ml histamine and normal saline, respectively). The elicited reactions were read after 15 minutes and were considered positive when the elicited wheal was ≥ 3 mm in diameter, provided that the negative control with normal saline was negative. All drugs susceptible of altering the tests results were withdrawn for ten days prior to the tests.

The specific IgE levels were quantified by the CAP System FEIA (Pharmacia Diagnostics, Uppsala, Sweden),



Fig. 1. Anaphylaxis: age-group and gender distribution.

according to the manufacturer's instructions. Values in excess of 0.35 kU/l were classed as positive.

Considering that, in patients with anaphylaxis, systemic reactions have been reported after skin tests, even by the prick method^{4,5}, it was preferred, whenever possible, to use the CAP procedure first for diagnostic confirmation.

When the cause of the reaction was still not evident after the detailed anamnesis, the following complementary tests were requested and performed on a routine basis: erythrocyte sedimentation rate, complete blood count, blood biochemistry assessment, skin prick tests with a panel of airborne allergens (*Dermatophagoides pteronyssinus*, grass pollens, olive pollen, *Artemisia vulgaris*, *Parietaria judaica*, *Plantago lanceolata*, *Chenopodium album*, *Alternaria alternata*, cat and dog epithelia), food allergens (cow's milk, egg, codfish, *Anisakis simplex*, shrimp, banana, peach, watermelon, honey, peanut, walnut, sunflower seeds, hazelnut, almond, pistachio, chestnut, wheat, soybean and mustard) and latex, *Echinococcus* serology, parasitologic study (ova and parasites) in faeces, complement fraction quantification (C₃ and C₄), total serum IgE, 5-indole-acetic acid excretion in 24-hour urine samples, and serum tryptase levels.

Considering the severity of the reactions reported by the patients, and for ethical reasons, intentional exposure to the suspected allergens was at all times avoided.

For the statistical study the χ^2 test on 2 x 2 contingency tables was used, with the Yates' correction when required.

RESULTS

A total of 1,450 patients were included in the study; the gender distribution was 820 (59.3%) females and 630 (40.7%) males; the ages ranged from 1 to 79 years, with a mean age of 25.9 years, a median of 20 years and a standard deviation of 18.9 years. A diagnosis of anaphylaxis was established in 58 cases, with an incidence rate of 4%

Table I. Anaphylaxis: aetiologies (by groups) in 58 patients

	No. of cases (percentage)
Drugs	36 (62)
Foods	14 (24.1)
<i>Hymenoptera</i>	5 (8.6)
Idiopathic	2 (3.4)
<i>A frigore</i>	1 (1.7)
Exercise-induced	1 (1.7)

among the total population of patients seen for the first time at our Allergology Clinic. Even though the female gender was predominant also in this group, with 32 female patients (55.2%), the difference in the gender distribution was not statistically significant. The mean age in the anaphylaxis group was 35.6 years, greater than that of the total sample studied and also greater among females (38.6 years) as compared to males (32 years). The greatest incidence rate occurred in the 25-to-45-year age group (Fig. 1). In our study, anaphylaxis was uncommon in childhood. In the female group an increase of the number of cases was seen from adolescence onwards and was then maintained.

Considering the aetiology, the highest incidence rate corresponded to drug reactions (62%), followed by food- and foodstuff-related reactions (24.1%), *Hymenoptera* venom allergy (8.6%), idiopathic cases (3.4%), and a single case each of exercise-induced anaphylaxis (1.7%) and urticaria *a frigore* (1.7%), the latter case occurring after a bath in cold water (Table I).

The drugs involved in the greatest numbers of anaphylaxis cases correspond to the following groups or families: β -lactam antibiotics (amoxycillin 15.5%, penicillin G 15.5%, cephazoline 3.4%, cefaclor 1.7%), non-steroidal antiinflammatory drugs (magnesium dipyron 13.7%, diclofenac 3.4%, naproxen 3.4%, ibuprofen 1.7% and propiphenazone 1.7%) and aminoglycoside antibiotics (streptomycin 6.8%) (Table II).

In order of diminishing frequency, the foods and foodstuffs causing anaphylaxis in our study were: honey 6.8%, legumes (lentil 6.8%, green bean 6.8%, pea 5.1%, haricot bean 5.1%, chickpea 5.1%, soybean 3.4%, lupin 1.7%) and nuts (sunflower seeds 5.1%, peanuts 3.4%, walnuts 1.7%, almonds 1.7%, hazelnuts 1.7%, pistachio 1.7%, chestnut 1.7%) (Table II).

Most of the patients with anaphylaxis due to *Hymenoptera* venom allergy were allergic to honeybee venom (6.8%), and only a single case was hypersensitive to wasp venom (1.7%) (Table II).

Table II. Antigens causing anaphylaxis in 58 patients

	No. of cases (percentage)
Drugs	
Amoxycillin	9 (15.5)
Penicillin G	9 (15.5)
Dipyrrone	8 (13.7)
Streptomycin	4 (6.8)
Cephazoline	2 (3.4)
Diclofenac	2 (3.4)
Naproxen	2 (3.4)
Cefaclor	1 (1.7)
Hyoscine	1 (1.7)
Lansoprazole	1 (1.7)
Mucopolysaccharides	1 (1.7)
Ibuprofen	1 (1.7)
Propiphenazone	1 (1.7)
Procaine	1 (1.7)
Foods	
Honey	4 (6.8)
Lentil	4 (6.8)
Green bean	4 (6.8)
Pea	3 (5.1)
Haricot bean	3 (5.1)
Chickpea	3 (5.1)
Sunflower seed	3 (5.1)
Peanut	2 (3.4)
Soybean	2 (3.4)
Egg	1 (1.7)
Chestnut	1 (1.7)
Walnut	1 (1.7)
Almond	1 (1.7)
Hazelnut	1 (1.7)
Pistachio	1 (1.7)
Lupin	1 (1.7)
Fish	1 (1.7)
Cow's milk	1 (1.7)
Pork kidney	1 (1.7)
<i>Hymenoptera</i> venoms	
Honeybee	4 (6.8)
Wasp	1 (1.7)

DISCUSSION

Anaphylaxis was the final diagnosis in 4% of the patients seen for the first time at our Allergy Clinic.

In the overall group there was no gender-associated predisposition, although this does occur for a number of concrete antigens because of the degree of exposure; thus, *Hymenoptera* venom allergy was more frequent among males while drug reactions were more frequent in females. A lower incidence rate was observed during childhood and among the aged population.

The mean age reported in a large U.S. series⁶ was 38 years, very similar to the mean age in our study.

Because of the rapidity with which the symptoms occur after exposure to the antigen and because of the severity of the clinical manifestations, which requires immediate medical help, the clinical history is fundamental for establishing a diagnostic suspicion. This suspicion diagnosis was obvious in most cases (96.6%) and could not be defined in only two (3.4%). It was possible to confirm the aetiological diagnosis in many cases through the quantification of antigen-specific IgE levels or through skin tests. The confirmation aetiological diagnosis in drug-induced anaphylaxis was more problematic, as the CAP test was positive for amoxycillin in only two cases, with values greater than 8 kU/l, in only one case for penicillin G (0.86 kU/l) and in one further case for procaine (1.8 kU/l). The CAP test for streptomycin, magnesium dipyrrone and diclofenac was always negative. However, all our patients with anaphylaxis caused by *Hymenoptera* venom allergy or food allergy had positive CAP results allowing confirmation of the diagnosis.

In 62% of the cases diagnosed of anaphylaxis, drugs were the aetiological agent. In our study, Plasencia 98-99, and within the context of drug allergy, anaphylaxis represented 17.1% of all drug-induced reactions. The two drug families of β -lactam antibiotics (particularly amoxycillin and penicillin G) and non-steroidal antiinflammatory drugs (mainly magnesium dipyrrone, a frequently-used pyrazolone both in outpatients and in the hospital setting in our environment) were the most frequent causes of anaphylaxis in the northern Extremadura area. It is worth noting that acetylsalicylic acid, which caused urticaria and angioedema in 10.8% of our adverse drug reaction patients, was not involved in any case of anaphylaxis. This suggests that the number of antigens able to trigger anaphylactic reactions is rather small, as it is restricted to those antigens having unique chemical characteristics that enable them to do so. This also holds valid in the case of food hypersensitivity, which in our study was associated with anaphylaxis in 14% of the patients. Although fruits (peach, watermelon, banana and others) were the foodstuffs causing the greatest number of cases of allergy, they were not involved in any episode of anaphylaxis, contrarily to other foodstuffs such as honey, legumes and nuts which often caused the most severe reactions. A similar phenomenon was seen among our patients with insect sting allergy, as only 17.2% of all those with *Hymenoptera* venom allergy developed anaphylaxis; even though there

were more patients who were hypersensitive to wasp venom (82.7%), anaphylactic reactions were more frequent among those who were hypersensitive to honeybee venom.

Skin prick tests and CAP tests with latex were performed to all patients with fruit allergy, and 24 of them evidenced positiveness. However, these were in most instances subclinical sensitisations; a number of cases had contact urticaria, and none of them had anaphylaxis.

Even though *Echinococcus* serologies were systematically performed to all patients with urticaria or anaphylaxis of uncertain origin, there were no positive cases. Over the last nine years we have diagnosed six cases of anaphylaxis due to rupture of *Echinococcus* cysts. This problem is thus infrequent, though it does exist.

The one case of exercise-induced anaphylaxis was food-dependent, with positive tests for nuts (peanut, walnut, pistachio and hazelnut), in a pollenosis patient.

The types of airborne allergens present in each geographic area has some bearing on food allergy. In our northern Extremadura region, 47% of our respiratory allergy patients were sensitised to the pollen of *Artemisia vulgaris*; this explains the high incidence rate of anaphylaxis to some foods such as honey, which contains pollens from plants of the *Compositae* family, or to foods that are antigenically related such as nuts, particularly sunflower seeds, pistachio⁷ and hazelnut⁸. This group also includes such "food allergy" causes as the direct ingestion of pollen and of camomile infusion⁷. All our previously mentioned food allergy patients had positive tests to *Artemisia vulgaris*, so that this pollen should be included in the study of idiopathic or uncertain-aetiology anaphylaxis.

Among our patients with rhinoconjunctivitis and/or asthma, 58.7% were sensitised to *Plantago lanceolata* pollen. We have established a correlation between allergy to this particular pollen and hypersensitivity to fruits of all types⁹, to some leaf vegetables and to latex. However, in this group of pollenosis patients these products usually cause milder clinical manifestations such as urticaria (usually of the contact type) and the oral allergy syndrome.

All our patients with anaphylaxis due to legume allergy reacted to several of them, thus underscoring the existence of cross-reactivity between these vegetables.

In the study of Kemp et al.⁶, contrary to our own, there was a high proportion of idiopathic anaphylaxis cases (37%), offset by a strikingly low one of anaphylactic drug reactions (20%). Among a childhood population,

Marguet et al.¹⁰ observed a 6.4% proportion of idiopathic forms and 42.5% of food-induced anaphylaxis. In our study area, however, drugs were the main cause of anaphylaxis (62%); this coincides with the results of other Spanish studies^{11,12}, which also point out β -lactam antibiotics and pyrazolones as the most relevant drug families. There is however a discrepancy regarding the foods and foodstuffs most frequently involved in anaphylaxis episodes: whereas for the Vitoria group the most frequently involved foodstuffs are *Anisakis simplex* and seafoods, and they have found not a single case caused by honey allergy, in our study honey and legumes were the causative agents most often identified and we did not see any case caused by *Anisakis simplex* allergy. In the studies mentioned, foods and foodstuffs were the second-ranking cause of anaphylaxis, followed by *Hymenoptera* venom allergy. The percentage rates for idiopathic anaphylaxis were low in both: 5.8%¹¹ and 4.8%¹².

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