ORIGINAL ARTICLE

Accuracy of the Diagnosis of Allergic Reactions in the Emergency Department

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Abstract

Background: Suspicion of an acute allergic reaction is a common reason for attending the emergency department (ED). However, there are few comparisons between the initial diagnosis of suspected allergic reaction made in the ED with the definitive diagnosis made subsequently in the allergy department (AD).
Objective: To compare details of the initial diagnosis made in the ED relating to allergy with the final diagnosis made in the AD.
Methods: Patients attending the ED of 2 hospitals with suspected allergic reactions were prospectively enrolled based on key words. A certified allergy specialist reviewed the ED records of these patients and, if these were suggestive of an allergic reaction, the patients were scheduled for further evaluation at the allergy clinic.
Results: In total, 2000 patients were enrolled between April 2013 and October 2015. Of these, 1333 passed the initial assessment and underwent further evaluation. Of the 1333 patients, 528 underwent an allergological study, and 206 were confirmed as being allergic. With respect to drug allergy, nonsteroidal anti-inflammatory drugs were the most common triggers, followed by β-lactams; in food allergy, plant-based foods were the most common. Only 16.4% of patients confirmed as having anaphylaxis in the AD were initially diagnosed with the condition in the ED.
Conclusion: Of the 528 patients who finally underwent the full allergological study, fewer than half were confirmed as allergic. Moreover, anaphylaxis appears to be underdiagnosed in the ED. Better communication between the ED and the AD is necessary to improve the diagnosis and management of these patients.

Key words: Anaphylaxis. Hypersensitivity drug reactions. Emergency medicine. Food allergy. Follow-up studies.

Resumen

Antecedentes: La sospecha de una reacción alérgica aguda es un motivo frecuente de consulta en urgencias. Sin embargo, hay pocos trabajos que comparen el diagnóstico inicial realizado en las unidades de urgencias con el diagnóstico definitivo realizado en las unidades de alergia.
Objetivo: Analizar en detalle la sospecha diagnóstica inicial dada en urgencias con el diagnóstico definitivo en las consultas de alergia.
Métodos: Estudio prospectivo, que consistió en la selección, en base a palabras claves, de pacientes con sospecha de reacción alérgica. En la fase de screening, se seleccionaron los pacientes en base a las palabras claves, finalmente aquellos pacientes que presentan reacción sugestiva de alergia se seleccionaron para evaluación final.
Resultados: Se revisaron 2.000 pacientes entre abril de 2013 y octubre de 2015, de los cuales 1.333 se seleccionaron para la evaluación. Finalmente, 528 se sometieron a un estudio alergológico y 206 se confirmaron como alérgicos. Con respecto a las reacciones por fármacos, los AINE y β-lactámicos fueron los mayormente implicados; en relación con los alimentos, los de origen vegetal fueron los más frecuentes. Sólo el 16,4% de los pacientes con anafilaxia confirmada tras el estudio de alergia, fueron diagnosticados inicialmente en urgencias.
Conclusión: Sólo la mitad de los pacientes que finalizaron en estudio fueron confirmados como alérgicos. Un dato importante es el infradiagnóstico de la anafilaxia en las urgencias. Por ello pensamos que es necesaria una mejor comunicación entre las unidades de urgencias y alergia para mejorar el manejo clínico y terapéutico de estos pacientes.

Palabras clave: Anafiaxia. Alergia a medicamentos. Urgencias. Alergia a alimentos. Estudio de seguimiento.

Introduction

Allergic reactions are acute medical events resulting from abnormal immunological hyperreactivity, generally to proteins or drugs. They generate a significant clinical burden in primary care departments. In the case of food allergy, common triggers include cow's milk, egg, wheat, soy, peanut, tree nuts, fish, shellfish, and fruits [1-2]. In the case of drug hypersensitivity reactions (DHRs), key triggers include nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics [3-4]. The clinical presentation of allergic reactions varies considerably. However, they are usually acute and severe, with urticaria, angioedema, and anaphylaxis being the most common signs [5-8].

Suspicion of allergic reactions is a major presenting complaint in the emergency department (ED). Allergic reactions generate significant costs for the health care system. In the USA, the estimated direct cost of food-induced allergic reactions and anaphylaxis was $227 million in 2007 [9]. Furthermore, recognition and treatment of anaphylaxis in the ED is often undermined by atypical presentation and a lack of adequate training among primary care physicians [10]. These concerns underline the need for better management of food allergy and DHRs by ED physicians.

Few studies have prospectively analyzed the diagnosis of patients presenting at the ED with a suspicion of allergy and subsequently compared those results with those of a standard outpatient evaluation by an allergist. Most previous studies focused on anaphylaxis [11-12]. Here, we used a multistep approach to screen ED patients for potential allergic reactions and compared the ED diagnosis with the final results from the allergology department. Our analysis was based on clinical characteristics and the most common triggers.

Methods

Study Design

We conducted a prospective study of patients aged ≥14 years who attended the ED of 2 hospitals in Málaga, Spain between April 2013 and June 2015. As an initial screening evaluation, the electronic medical records of patients who sought assistance at either of the EDs were screened for specific key words. In the next step (primary evaluation), a certified allergist analyzed the ED electronic medical records of the patients who underwent the screening evaluation and contacted them by telephone to obtain additional details. Those suspected of having experienced an allergic reaction proceeded to the last step (final evaluation), which involved an extensive allergological work-up in our unit by 1 of 2 certified allergists who were not involved in the primary evaluation (Figure).

Data collected by the ED physician from patients selected in the screening evaluation were compared with those obtained from patients selected in the primary evaluation. Data from patients selected in the primary evaluation were also compared with those obtained from the allergological work-up in the final evaluation.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Provincial Investigational Ethics Committee of Malaga. All the participants were informed orally about the allergological work-up and signed the corresponding informed consent document.

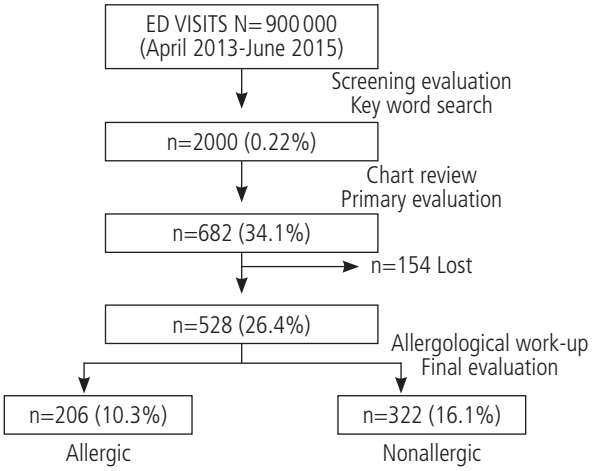

Figure. Flow chart for patients included in the study.

Screening Evaluation (Key Word Search)

The reason for consultation and the final diagnosis at the ED visit were screened for a possible match to a predetermined key word bank (*allergy, hypersensitivity, allergic reaction, urticaria, cutaneous eruption, infection, dermatitis, exanthema, anaphylaxis, reaction, angioedema, adverse event, insect sting, erythema, pruritus, drug intolerance, asthma*, and *food intoxication*) to search for possible allergic diseases.

Primary Evaluation

A single, certified allergist performed the primary evaluation within 10 days of the ED visit. Patients with a suspected allergic reaction (suggestive symptoms and/or suggestive time interval between allergen contact/intake and reaction) were selected. A standardized data collection form was used to record demographical and clinical data, including allergy and asthma history, identification of the number and the type of culprit allergens, timing of the reaction, presenting signs and symptoms, and management by an ED physician. The diagnosis as reported by the ED physician was categorized into one of the following groups: food allergy, DHR, food plus drug allergy, dermatological disease, other allergy, angioedema (without urticaria), idiopathic urticaria, and other diseases.

Final Evaluation

All patients selected in the first evaluation were offered an allergological work-up at the outpatient Allergy Unit. This formal evaluation was initiated within 4 weeks of the ED visit and completed by a different allergist to the one who performed the primary evaluation. If necessary, we performed skin prick tests (SPTs), intradermal tests (IDTs), measurement of specific IgE (sIgE) by ImmunoCAP (Thermo Fisher Scientific), the basophil activation test (BAT), double-blind placebo-controlled food challenge (DBPCFC), and/or single-blind placebo-controlled drug provocation test (DPT).

Diagnosis of anaphylaxis was based on the European Academy of Allergy and Clinical Immunology (EAACI) guidelines [13]. Participants with DHR were classified according to previous guidelines [14-15]. They were also classified based on the time to response as immediate responders (<1 hour after drug administration) or nonimmediate responders (>1 hour).

Skin Testing

Food allergy was investigated using SPT performed according to European guidelines [16] with commercialized allergen extracts (ALK-Abelló). The response was considered positive if the diameter of the wheal was 3 mm greater than the saline control. DHR was investigated using SPT with the culprit drug and, if the result was negative, by IDT, as recommended. The dosages for the different drugs were as described previously [17].

In Vitro Testing

sIgE levels were determined by ImmunoCAP following the manufacturer's recommendations. Results were expressed as kU_A/L and considered positive when >0.35 kU_A/L [18]. BAT was performed as described [19], including different concentrations of the suspected allergen or drug. The results were presented as the percentage of activated basophils ($CD63^+CD203c^+CCR3^+$).

Provocation Test

Food allergy was investigated using DBPCFC performed at the Allergy Unit following EAACI recommendations [20]. Blinded active and placebo meals were randomly administered on separate days and prepared immediately before the challenge. Up to 5 doses were administered at 20-minute intervals until the intended cumulative dose was reached. After the last dose, the patient remained in observation for at least 2 hours.

DHR was investigated using DPT performed at the Allergy Unit. If negative, a 2-day course of outpatient therapy with the culprit drug was administered as described elsewhere [19,21].

Table 1. Search Results Using Screening Key Words During the Primary Evaluation

Key Word	No. (%)
Allergic reaction	992 (49.6)
Urticaria	496 (24.8)
Cutaneous eruption	156 (7.8)
Infection	78 (3.9)
Dermatitis	44 (2.2)
Exanthema	44 (2.2)
Anaphylaxis	40 (2.2)
Reaction	34 (1.7)
Angioedema	32 (1.6)
Adverse event	24 (1.2)
Insect sting	14 (0.7)
Erythema	12 (0.6)
Pruritus	10 (0.5)
Drug intolerance	8 (0.4)
Asthma	6 (0.3)
Food intoxication	6 (0.3)
Anaphylactic shock	4 (0.2)

Statistical Methods

Confidence intervals for descriptive data were calculated using a modified Wald method. The 2-tailed Fisher exact test was used to analyze nominal variables. Means between groups were compared using paired *t* tests. Agreement on diagnosis between 2 observers was quantified using the Cohen κ statistic. All analyses were performed using GraphPad PRISM version 6.0b (GraphPad).

Results

Our ED department provides care for approximately 450 000 patients each year; most of these patients live in the province of Malaga. Two thousand patients (0.22% of

Table 2. Demographic Characteristics and Allergy History

Characteristics	No.	(%)
Participants, No.	2000	
Mean age, y	39.2 (38.2-40.1)	
Women, No, %	1196	59.8
Allergy history	672	33.6
Aeroallergens	302	15.1
Pollen	166	54.9
Dust mite	124	41.1
Pet dander	62	20.5
Mold	8	2.6
Unidentified	86	28.5
Food	126	6.3
Fish	10	7.9
Crustacean	26	20.6
Mollusk	28	22.2
Tree nuts	48	38.1
Fruits and vegetables	70	55.5
Legumes	2	1.58
Milk	4	3.2
Egg	2	1.6
Cereal and soya	6	4.7
Other	4	3.1
Drugs	340	17
β-Lactam	122	35.8
Quinolone	14	4.1
Macrolide	10	2.9
Sulfamide	24	7.1
Other antibiotics	14	4.1
NSAID	140	41.2
Radiocontrast media	18	5.29
Other drugs	72	21.2

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

the total number of patients evaluated in the ED) met the inclusion criteria for the screening phase and were analyzed in the primary evaluation. The results of the search for a match between the ED physician diagnosis and predetermined key words are shown in Table 1. Most of the patients evaluated were women (59.8%), and the median (IQR) age was 39.2 (38.2-40.1) years. Of these, 302 patients (15.1%) had a clinical history of atopy, 166 (54.9%) were sensitized to pollen, 124 (41.1%) to dust mite, 62 (20.5%) to pet dander, and 8 (2.65%) to mold; 216 (10.8%) patients had a history of asthma. The demographic and clinical characteristics of the initial 2000 patients are shown in Table 2. All patients were contacted

Table 3. Comparison of the Results of the Primary Evaluation

Characteristics	Not Studied, No.	(%-SD)	Selected, No.	(%-SD)	*P*
Participants	1472	73.5	528	26.4	
Mean (SD) age, y	39	(38.1-44.3)	39.5	(39-45)	.721
Female	844	57.3	352	66.7	.008
Asthma history	144	9.8	72	13.6	.105
Allergy history	426	28.9	246	46.6	<.0001
Aerollergens	172	11.7	130	24.6	<.0001
Food	76	5.2	50	9.5	.018
Drug	240	16.3	100	18.9	.340
Other	18	1.2	12	2.3	.242
Presumptive diagnosis					
DHR	388	26.4	218	41.3	<.0001
Food allergy	362	24.6	138	26.1	.62
Food and drug allergy	38	2.6	18	3.4	.515
Other allergy	124	8.4	30	5.7	.179
Dermatology	252	17.1	22	4.2	<.0001
Idiopathic urticaria	240	16.3	96	18.2	.502
Clinical presentation					
Anaphylaxis	112	7.6	66	12.5	.023
Dermatitis	114	7.7	14	2.7	.003
Erythema	96	6.5	30	5.7	.768
Exanthema	154	10.5	46	8.7	.474
Pruritus	28	1.9	8	1.5	.794
Undefined rash	110	7.5	24	4.5	.115
Airway symptoms	76	5.2	36	6.8	.349
Urticaria/angioedema	658	44.7	144	54.5	.006
Vesicles	36	2.4	4	0.8	.12
Undefined	26	1.8	6	1.1	.581
Suspected triggers					
Drug					
β-Lactam	126	8.6	72	14.4	.009
Quinolone	32	2.2	14	2.7	.637
Macrolide	14	1.0	6	1.1	.729
Sulfamide	6	0.4	2	0.4	1
Other antibiotics	42	2.9	18	3.4	.675
NSAID	224	15.2	138	26.1	<.0001
Radiocontrast media	2	0.1	8	1.5	.019
Food					
Fish	100	6.8	36	6.8	1
Crustacean	64	4.3	30	5.7	.398
Mollusk	54	3.7	14	2.7	.554
Tree nut	32	2.2	18	3.4	.26
Fruit and vegetable	132	9.0	60	11.4	.273
Legume	12	0.8	2	0.4	.683
Milk	22	1.5	8	1.5	1
Egg	40	2.7	14	2.7	1
Cereal and soya	46	3.1	24	4.5	.328
Other food	28	1.9	16	3.0	.327
No food or drug	176	12.0	22	4.2	.0002

Abbreviations: DHR, drug hypersensitivity reaction: NSAID, nonsteroidal anti-inflammatory drug.

by phone for the primary evaluation. A total of 1333 met the inclusion criteria; 199 (9.95%) did not meet these criteria and were excluded, as there was no suspicion of allergy, and 468 (23.4%) could not be contacted. Of the 1333 patients who underwent the primary evaluation, 805 (60.3%) chose not to participate further in the study. The remaining 528 patients (39.6%) patients underwent a complete allergological work-up (Figure).

A comparison of patients who underwent the final allergological work-up with those who did not complete the full process for various reasons revealed gender differences. A higher proportion of females underwent the final studies (*P*=.008). In addition, women were also more likely to have a prior history of allergy (*P*<.0001)—specifically to aeroallergens (*P*<.0001)—a presumptive diagnosis of DHR (*P*<.0001), anaphylaxis (*P*=.023), and specific triggers such as β-lactams (*P*=.009), NSAIDs (*P*<.0001), and contrast media (*P*=.019). All comparisons are detailed in Table 3.

Among participants who underwent the allergological work-up, 40.9% were diagnosed with idiopathic urticaria. Food allergy was recorded in 86 patients (16.3%), of whom 24 (28.6%) had previously been diagnosed as allergic to the food that caused the ED visit. Among these 86 food-allergic patients, 84 (97.6%) had reactions triggered only by food, whilst 2 (2.4%) presented a reaction that could be attributed to both food and drugs (lipid transfer protein and amoxicillin). For these 86 participants, diagnosis was achieved by SPT (72.1%) and determination of sIgE (27.9%). The clinical presentation was urticaria and angioedema for 32 individuals (37.2%), anaphylaxis for 26 (30.2%), and upper or lower airway symptoms in 16 (18.6%). Fruits and vegetables were the most prevalent triggers, inducing reactions in 34 patients (39.5%), followed by crustaceans in 20 patients (23.2%) and cereals in 16 patients (18.6%).

Table 4. Differences Between the Primary and Final Evaluation by a Trained Allergist For 86 Food-Allergic Participants

	Primary Evaluation	Final Evaluation	*P*
Diagnosis, No. (%)			
Food allergy	62 (72.2)	84 (97.7)	.002
Food and drug allergy	12 (14)	2 (2.3)	.109
Other allergy	6 (7)	0	.241
Dermatology	2 (2.3)	0	1
Idiopathic urticaria	4 (4.7)	0	.494
Clinical presentation			
Anaphylaxis	26 (30.2)	48 (55.8)	.023
Erythema	6 (7)	2 (2.3)	.616
Undefined rash	4 (4.7)	0	.494
Upper or lower airways symptoms	16 (18.6)	18 (20.9)	1
Urticaria and/or angioedema	32 (37.2)	18 (20.9)	.152
Undefined	2 (2.3)	0	1
Trigger			
Fish	8 (9.3)	0	.116
Crustacean	20 (23.3)	26 (30.2)	.625
Mollusk	8 (9.3)	6 (7)	1
Tree nut	10 (11.6)	18 (20.9)	.381
Fruit and vegetables	34 (39.5)	46 (53.5)	.076
Legume	0	6 (7)	.241
Milk	6 (7)	2 (2.3)	.616
Egg	6 (7)	0	.241
Cereal and soya	16 (18.6)	0	.005
Meat	10 (11.6)	0	.055
Anisakis	0	4 (4.6)	.056
Other food	6 (7)	2 (2.3)	.616
Drug	14 (16.3)	2 (2.3)	.057
Other	2 (2.3)	0	1

Comparison of the data after the final evaluation with those obtained from the primary evaluation showed an increase in the percentage of cases confirmed as anaphylaxis (54.8% vs 28.6%; *P*=.026) and in the percentage of reactions induced by fruit and vegetables (39.5% vs 53.5%; *P*=.036), as well as a decrease in the percentage of reactions induced by cereal (18.6% vs 0.0%; *P*=.005) (Table 4).

Of the patients who underwent an allergological work-up, 116 (22.0%) were confirmed as having a DHR. Clinical symptoms reported by patients were, in descending order, anaphylaxis (46 [40.4%]), urticaria/angioedema (44 [38.6%]), and exanthema (18 [15.8%]). A total of 94 patients (81.0%) reported an immediate reaction and 22 (19.0%) a nonimmediate reaction. Most patients (114 [98.3%]) reported reactions to only 1 drug; 2 patients (1.7%) had a concomitant reaction after the intake of 2 different drugs: acetaminophen and ibuprofen in both cases. The most frequent triggers were NSAIDs, affecting 72 patients (62.1%), followed by β-lactams in 26 patients (22.4%) and quinolones and radiocontrast media in 6 patients (5.2%). The comparison of data after the final evaluation with those obtained from the primary evaluation showed an increase in the percentage of cases reporting only 1 culprit drug (87.7% vs 98.3%; *P*=.032). No statistically significant differences were found when clinical symptoms, timing of the reaction, and identified triggers were analyzed (Table 5).

Among the 72 patients with confirmed hypersensitivity to NSAIDs after the final evaluation, 12 (16.7%) were already known to be NSAID-hypersensitive before their ED visit. Seventy patients were diagnosed by DPT; 2 were diagnosed by SPT to dipyrone. The clinical presentation reported after NSAID intake was urticaria/angioedema (32 [44.4%]), followed by anaphylaxis (30 [41.6%]), exanthema (4 [5.6%]), fixed drug eruption (2 [2.8%]), and upper airway symptoms (2 [2.8%]). The final diagnoses were confirmed as single NSAID–induced urticaria/angioedema or anaphylaxis (46 [63.9%]), NSAID-induced urticaria/angioedema (18 [25.0%]), NSAID-induced delayed hypersensitivity reactions (6 [8.3%]), or NSAID-exacerbated respiratory disease (2 [2.8%]). Dipyrone was the most common trigger, affecting 38 patients (52.8%), followed by propionic acids (namely ibuprofen) in 14 patients (19.4%), naproxen in 6 patients (8.3%), dexketoprofen in 4 patients (5.6%), diclofenac in 8 patients (11.1%), and aspirin in 2 patients (2.8%).

Among the 26 patients confirmed as having β-lactam allergy, 4 (15.4%) were already known to be hypersensitive to β-lactams before the ED visit. Diagnosis was established by IDT for 14 (53.8%) patients, BAT for 4 (15.4%), and DPT for 8 (30.8%). The clinical presentation after β-lactam intake—as

Table 5. Differences Between the Primary and Final Evaluation by a Trained Allergist For 116 Drug-Allergic Participants

	Primary Evaluation	Final Evaluation	*P*
Diagnosis, No. (%)			
DHR	106(93)	116 (98.3)	.206
Food allergy	2 (1.8)	0	1
Food and drug allergy	6 (5.3)	2 (1.7)	.618
Other allergy	2 (1.8)	0	1
Dermatology	0	0	1
Idiopathic urticaria	0	0	1
Other	0	0	1
Clinical presentation			
Anaphylaxis	26 (22.8)	46	.070
Erythema	10 (8.8)	2 (1.7)	.206
Pruritus	2 (1.8)	2 (1.7)	1
Undefined rash	10 (8.8)	2 (1.7)	.206
Upper or lower airway symptoms	4 (3.5)	2 (1.7)	1
Urticaria and/or angioedema	50 (43.9)	44 (37.9)	.706
Exanthema	14 (12.3)	18 (15.5)	.787
Undefined	0	0	1
Mechanism identified			
Immediate reaction	94 (82.5)	94 (81)	1
Nonimmediate reaction	20 (17.5)	22 (19)	1
Undefined	2 (1.8)	0	1
Number of drug triggers			
One	100 (87.7)	114 (98.3)	.032
Two	10 (8.8)	2 (1.7)	.206
Three and more	4 (3.5)	0	.496
Not identified	2 (1.8)	0	1
Trigger			
β-Lactam	28 (24.6)	26 (22.4)	1
Quinolone	6 (5.3)	6 (5.2)	1
Macrolide	0	0	1
Sulfamide	0	0	1
Other antibiotics	4 (3.5)	0	.496
NSAID	72 (63.2)	72 (62.1)	1
Radiocontrast media	6 (5.3)	6 (5.2)	1
Other drug	12 (10.5)	6 (5.2)	.49
Food	8 (7)	2 (1.7)	.364
No food or drug	0	0	1

Abbreviations: DHR, drug hypersensitivity reaction; NSAID, nonsteroidal anti-inflammatory drug.

reported by patients—was anaphylaxis in 10 cases (38.5%), followed by urticaria/angioedema in 8 (30.8%), exanthema in 4 (15.4%), pruritus in 2 (7.7%), and erythema in 2 (7.7%). The culprit drug after the primary evaluation was amoxicillin-clavulanate for all participants. After the allergological work-up, 12 cases (46.2%) were confirmed as having selective allergy to amoxicillin, 10 patients (38.5%) as having selective allergy to clavulanic acid, and 4 (15.4%) patients as having cross-reactive allergy to β-lactams.

Of the 528 who underwent an allergological work-up, 206 (39%) had their suspected allergy trigger confirmed, 96 (18.1%) were actually allergic to a different causal agent, and 2 (0.3%) were diagnosed with idiopathic anaphylaxis and mastocytosis. No allergic trigger was identified in 8 patients (1.5%).

Among the patients who underwent an allergological work-up, 110 (20.8%) met the criteria for anaphylaxis. Of these, 48 (43.6%) had anaphylaxis caused by food allergy due to (in descending order) fruits and vegetables (16 [14.5%]), crustaceans (14 [12.7%]), tree nuts (6 [5.5%]), *Anisakis* (4 [3.6%]), peanuts (4 [3.6%]), milk (2 [1.8%]), and mustard (2 [1.8%]). In the case of patients who developed an anaphylactic reaction induced by drugs (46 [41.8%] of the total 110 cases of anaphylaxis), the culprits were (in descending order) NSAIDs in 32 patients (29.1%), β-lactams in 12 (10.9%), and quinolones in 2 (3.6%). Among patients with hypersensitivity to NSAIDs, 26 (23.6%) were confirmed as having single NSAID–induced urticaria/angioedema or anaphylaxis and 6 (5.5%) as having NSAID-induced urticaria/angioedema. In the case of β-lactam allergy, 4 patients (3.6%) were diagnosed as having cross-reactivity to β-lactams, 4 (3.6%) a selective allergy to amoxicillin, and 2 (1.8%) a selective allergy to clavulanic acid. Eight patients (7.3%) were diagnosed with idiopathic anaphylaxis and anaphylaxis induced by hymenoptera venom, latex allergy, exercise-induced allergy, and mastocytosis (1.8%, respectively) (Supplementary Table 1).

Of the 110 patients who met the criteria for anaphylaxis, only 18 (3.8%) were diagnosed as such in the ED. Moreover, inpatient treatment by ED physicians included epinephrine in 20 cases (18.8%), antihistamines in 82 (74.5%), and systemic corticosteroids in 88 (80%). Upon discharge, prescribed treatment included self-injectable epinephrine in 8 patients (7.2%), antihistamines in 90 (81.8%), and systemic corticosteroids in 48 (43.2%) (Supplementary Table 2).

Agreement on diagnosis between ED physicians, trained allergists in the primary evaluation, and trained allergists in the final evaluation was measured using the Cohen κ statistic for all 528 fully evaluated cases. A concordant result was found between the ED physician and the allergist after the final evaluation in 246 of the 528 cases (46.6%; κ=0.325 [0.254-0.396]); a concordant result was found between the allergist in the primary evaluation and the other allergist in the final evaluation for 282 of the 528 cases (53.41%; κ=0.413 [0.343-0.482]).

Discussion

We assessed all patients attending the ED over a 2-year period using a key word–based screening evaluation, which yielded 2000 patients with a potential allergic disease. After excluding patients who were clearly not allergic, could not be contacted, or chose not to participate further, the final sample comprised 528 patients who completed the allergological work-up. These were mainly diagnosed with idiopathic urticaria (40.9%), DHR (22.0%), food allergy (16.3%), and dermatological conditions (10.2%).

Most of the initial 2000 participants were not assessed; in fact, only 26.4% completed the study. This relatively low rate of completion limits the power of the study, including

the identification of statistically significant differences in characteristics such as allergen type. In addition to the 199 patients who were clearly not allergic and thus excluded at the primary evaluation, other patients did not complete the study owing to problems making and maintaining contact, as well as for reasons such as lack of interest, work commitments, and prohibitive distance.

We compared demographic and clinical information between patients who were not studied and those who finally underwent the allergological work-up and found that women were more prone to be investigated. This is a well-documented phenomenon for various medical conditions [22-23]. Interestingly, many of the patients diagnosed with anaphylaxis in the allergological work-up were diagnosed with urticaria/angioedema in the ED. It may be the case that patients who themselves suspect a more severe reaction are more likely to attend their allergological work-up. On the other hand, a milder allergic presentation may discourage completion of the study; for example, a much higher percentage of dermatological disease was observed in patients who did not complete the assessment than in those who underwent the allergological work-up (Table 2). Similarly, patients with DHRs, especially those reacting to NSAIDs and β-lactams, were more likely to undergo the final allergological work-up. This phenomenon could be explained by the lack of knowledge regarding these prevalent drug allergies in the study population, or perhaps the lack of alternative medicines means patients are keener to attend their appointments. This is an important point, as for many drugs, such as β-lactams, resistance and cost of alternatives are a major issue [24].

Nonetheless, when we compared the prevalence of NSAID and β-lactam allergy, our results were similar to those of other authors [25]. More studies are necessary in EDs in other geographical locations before these findings can be extrapolated to the general population.

Furthermore, anaphylaxis was identified in 20.8% of the 528 participants who completed the allergological work-up. The condition was diagnosed through analysis of the clinical history based on the EAACI guidelines [26]. Food allergy and DHR accounted for 43.6% and 41.8%, respectively, of all anaphylaxis cases. The prevalence of food anaphylaxis found here agrees with that reported in other studies, ranging from 31.0% to 51.0% [27-28]. However, the prevalence of drug-induced anaphylaxis appears to be slightly higher in our population, possibly owing to higher drug consumption or demographic differences. NSAIDs were most frequent culprits in the present study, consistent with data reported elsewhere [29-30].

Of the 528 patients finally evaluated in the allergological work-up, 110 were confirmed as having anaphylaxis. However, the term anaphylaxis was used in only 3.8% of electronic medical records in the ED. This is consistent with the finding that only 18.1% of the 110 confirmed patients with anaphylaxis were treated with epinephrine according to guidelines whilst in the ED. Moreover, less than half of these patients were discharged with a prescription for self-injectable epinephrine. In fact, various studies have shown that erroneous identification of anaphylaxis is a real issue in the ED and that around 57% of cases may be misdiagnosed and up to 80% undertreated [31-33]. Given that timely administration of epinephrine is essential for the effective treatment of anaphylaxis and that such treatment is dependent on the correct identification of cases, better training of ED physicians and better collaboration with the allergology department will ensure prompt recognition and better management [10].

Analysis of agreement on diagnosis between the final evaluation from the allergology department and the initial primary evaluations and evaluations by ED physicians showed a moderate and fair correlation, respectively, with concordance values of 53.4% and 46.6%. Since primary evaluation depends on data available in electronic medical records, this is likely to explain the discrepancy between the primary and final evaluations, even though both are made by certified allergists. Interestingly, the trigger was not identified during the ED visit in 19.8% of the patients who underwent the allergological work-up. However, the complexity of identifying the trigger of an acute allergy reaction is well known [34], and this finding should not necessarily be considered a deficiency of the ED.

After the final evaluation, only 69.72% of patients initially diagnosed with drug allergy and 76.24% of those diagnosed with food allergy in the ED were confirmed as nonallergic. In other words, a large percentage of patients are being overdiagnosed and therefore unnecessarily advised to avoid certain drugs and foods.

In summary, our results highlight the importance of educating primary care physicians about the clinical presentations of allergy, particularly with regards to anaphylaxis and its appropriate treatment with epinephrine. Similarly, food allergy and DHRs should be thoroughly assessed by a trained allergist in order to correctly identify triggers.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Murano A, Sheikh A, et al. Prevalence of common food allergen in Europe: a systematic review and meta-analysis. Allergy. 2014;69:992-1007.
2. Fernandez-Rivas M, Bolhaar S, Gonzalez-Mancebo E, Asero R, van Leeuwen A, Bohle B, et al. Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods. J Allergy Clin Immunol. 2006;118:481-8.
3. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105:259-73.
4. Aun MV, Blanca M, Garro LS, Ribeiro MR, Kalil J, Motta AA, et al. Nonsteroidal anti-inflammatory drugs are major causes of drug-indiced anaphylaxis. J Allergy Clin Immunol Pract. 2014;2:414-20.
5. Cervellin G, Schirosa F, Buonocore R, Nouvenne A, Borghi L, Meschi T, et al. Spring season birth is associated with higher emergency department admission for acute allergic reactions. Eur J Intern Med. 2016;2:97-101.
6. Ruffoni S, Furgani A, Schiavetti I, Ciprandi G. Anaphylaxis: a one-year survey on Medical Emergency Service in Liguria (Italy). Eur Ann Allergy Clin Immunol. 2015;47:86-90.
7. Dyer AA, Lau CH, Smith TL, Smith BM, Gupta RS. Pediatric emergency department visits and hospitalizations due to food-induced anaphylaxis in Illinois. Ann Allergy Asthma Immunol. 2015;115:56-62.
8. Minale P, Bignardi D, Troise C, Voltolini S, Dignetti P. A regional approach to unmet needs in anaphylaxis. Eur Ann Allergy Clin Immunol. 2016;48:88-93.
9. Patel D, Holdford D, Edwards E, Carrol N. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. J Allergy Clin Immunol. 2011;128:110-5.
10. Campbell R, Li J, Nicklas R, Sadosty A. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol. 2014;113:599-608
11. Alvarez-Perea A, Tomás-Pérez M, Martínez-Lezcano P, Marco G, Pérez D, Zubeldia JM, et al. Anaphylaxis in Adolescent/Adult Patients Treated in the Emergency Department: Differences between Initial Impressions and the Definitive Diagnosis. J Investig Allergol Clin Immunol. 2015;25:288-94.
12. Moro Moro M, Tejedor Alonso MA, Esteban Hernández J, Múgica García MV, Rosado Ingelmo A, Vila Albelda C. Incidence of Anaphylaxis and Subtypes of Anaphylaxis in a General Hospital Emergency Department. J Investig Allergol Clin Immunol. 2011;21:142-9.
13. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernandez-Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014;69:1026-45.
14. Ariza A, Mayorga C, Salas M, Doña I, Martín-Serrano A, Pérez-Inestrosa E, et al. The influence of the carrier molecule on amoxicillin recognition by specific IgE in patients with immediate hypersensitivity reactions to betalactams. Scientific Reports. 2016;6:35-113.
15. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013;68:1219-32.
16. Dreborg S, Frew A. Position Paper: Allergen Standardization and skin tests. Allergy. 1993;4848-82.
17. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68:702-12.
18. Bazaral H, Hamburger RN. Standardization and stability of immunoglobulin E (IgE). J Allergy Clin Immunol. 1972;49:189-91
19. Torres MJ, Padial A, Mayorga C, Fernández T, Sanchez-Sabate E, Cornejo-Garcia JA, et al. The diagnostic interpretation of basophil activation test in immediate allergic reactions to betalactams. Clin Exp Allergy. 2004;34:1768-75.
20. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology. Allergy. 2004;59:690-7.
21. Ortega N, Doña I, Moreno E, Audicana MT, Barasona MJ. Practical guidelines for diagnosing hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. J Investig Allergol Clin Immuno. 2014;24:308-23.
22. Pattyn E, Verhaeghe M, Bracke P. The gender gap in mental health service use. Soc Psychiatry Psychiatr Epidemio. 2015;50:1089-95.
23. Yousaf O, Grunfeld EA, Hunter MS. A systematic review of the factors associated with delays in medical and psychological help seeking among men. Health Psychol Rev. 2015;9:264-76.
24. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol. 2014;133:790-6.
25. Jares E, Sanchez-Borges M, Cardona-Villa R, Ensina L, Arias-Cruz A, Gómez M, et al. Multinational experience with hypersensitivity drug reactions in Latin America. Ann Allergy Asthma Immunol. 2014;113:282-9.
26. MuraroT, Werfel K, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. Allergy. 2014;1008-25.
27. Campbell R, Park M, Kueber M, Lee S, Hagan J. Outcomes of Allergy/immunology follow-up after emergency department evaluation for anaphylaxis. J Allergy Clin Immunol Pract. 2015;3:88-93.
28. Clark S, Bock SA, Gaeta T, Brenner B, Cydulka RK, Camargo CA, et al. Multicenter study of emergency department visits for food allergies. J Allergy Clin Immunol. 2004;113:347-52.
29. Aun MV, Blanca M, Garro LS, Ribeiro MR, Kalil J, et al. Nonsteroidal anti-inflammatory drugs are major causes of drug-indiced anaphylaxis. J Allergy Clin Immunol Pract. 2014;2:414-20.
30. Jares E, Sanchez-Borges M, Cardona-Villa R, Ensina L, Arias-Cruz A, Gómez M, et al. Multinational experience with hypersensitivity drug reactions in Latin America. Ann Allergy Asthma Immunol. 2014;113:282-9.

31. Klein JS, Yocum MW. Under reporting of anaphylaxis in a community emergency room. J Allergy Clin Immunol. 1995;95:637-8.
32. Campbell RL, Luke A, Weaver AL, St Sauver JL, Bergstralh EJ, Li JT, Manivannan V, et al. Prescriptions for self-injectable epinephrine and follow-up referral in emergency department patients presenting with anaphylaxis. Ann Allergy Asthma Immunol. 2008;101:631-6.
33. Campbell RL, Hagan JB, Manivannan V, Decker W, Kanthala A. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. J Allergy Clin Immunol. 2012;129:748-52.
34. Webb LM, Liberman P. Anaphylaxis: a review of 601 cases. Ann Allergy Asthma Immunol. 2006;97:39-43.

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