

Significance of Infrequent and Unspecific Pathologies Recorded in the Spanish Survey *Alergológica-2005*

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■ Abstract

Background: There are infrequent or unspecific diseases that occupy an important part of time in the job of the allergists.

Objective: We sought to evaluate the frequency and to determine the characteristics of uncommon or unspecific diseases seen by allergists in Spain, and to compare these data with findings obtained in a similar study undertaken in 1992.

Material and Methods: An observational, prospective and cross-sectional study named "*Alergológica 2005*" was carried out in Spain. A part of this study analyzed the demographic, healthcare and clinical aspects of infrequent or unspecific diseases categorized as "Other allergic diseases" (OAD) or "Other non-allergic diseases" (ONAD).

Results: The survey comprised 4991 patients. In OAD, 45 patients were included. In ONAD, 290 patients were included. Significant diagnoses were gastroallergic anisakiasis (10 patients), idiopathic anaphylaxis (7 patients), and hypersensitivity pneumonitis (2 patients). In the ONAD group, non allergic respiratory diseases were the most frequent diagnosis. Mean time spent to reach a diagnosis was 14.2 days. However, the median of this time was only 1 day. Main diagnostic methods employed were a clinical history/physical examination in 86% of patients and skin tests in 73.7%.

Conclusion: Several unspecific diseases affected more than 60% of patients in the two groups together. Findings show the current knowledge of allergic disorders due to Anisakis simplex. Diagnoses of hypersensitivity pneumonitis seem to be as frequent as previously published. Idiopathic anaphylaxis seems to be less frequent. The wide-range of times needed to reach a diagnosis was in agreement with the mixture of diseases included in both groups.

Key words: Allergy. Epidemiology. Cross-sectional study. Other allergic diseases. Other non-allergic diseases. Gastroallergic anisakiasis. Hypersensitivity pneumonitis. Anaphylaxis. Alergologica.

■ Resumen

Antecedentes: Enfermedades infrecuentes o inespecíficas ocupan una parte importante del trabajo diario de los alergólogos. Objetivos: Evaluar la frecuencia y las características de ciertas enfermedades poco comunes o inespecíficas asistidas por los alergólogos españoles; y comparar estos hallazgos con los obtenidos en un estudio similar de 1992. Material y métodos: Se realizó en toda España un estudio prospectivo y transversal, llamado "*Alergológica 2005*". Una parte del estudio analizaba aspectos demográficos, sanitarios y clínicos de ciertas enfermedades clasificadas como "otras enfermedades alérgicas" (OEA) y "otras enfermedades no-alérgicas" (OENA).

Resultados: Se implicaron a 4.991 pacientes en el estudio. De ellos, 45 pacientes se clasificaron dentro del grupo de OEA, y 290 pacientes en el grupo de OENA. Los diagnósticos más significativos fueron Anisakiasis Gastroalérgica (10 pacientes), anafilaxia idiopática (7 pacientes) y neumonitis de hipersensibilidad (2 pacientes). Dentro del grupo de OENA, las enfermedades respiratorias no alérgicas fueron el diagnóstico más frecuente. Para llegar al diagnóstico final se precisaron 14.2 días de media. Sin embargo, la mediana de ese tiempo fue de sólo 1 día. Los principales métodos diagnósticos empleados fueron: historia clínica/examen físico en el 86% de pacientes y pruebas cutáneas en el 73.7%.

Conclusión: Varias enfermedades inespecíficas afectaron a más del 60% de los pacientes en los 2 grupos juntos. Los resultados demuestran el conocimiento actual de los enfermedades alérgicas atribuidas al Anisakis simplex. Los diagnósticos de neumonitis de hipersensibilidad parecen ser tan frecuentes como se ha publicado previamente. La anafilaxia idiopática parece ser menos frecuente. La amplia variedad de tiempos empleados para el diagnóstico estuvo en concordancia con la mezcla de las enfermedades incluidas en los ambos grupos estudiados.

Palabras clave: Alergia. Epidemiología. Estudio transversal. Otras enfermedades alérgicas. Otras enfermedades no-alérgicas. Anisakiasis gastroalérgica. Neumonitis de hipersensibilidad. Anafilaxia. Alergologica.

Introduction

The prevalence of allergic diseases and allergic sensitization has been increasing over the last half century and this trend has been well documented in highly developed countries and has been associated with so-called westernized style of life.

In 1992, the Spanish Society of Allergy and Clinical Immunology started a trial in order to obtain accurate information on the epidemiologic, clinical and socioeconomic characteristics of allergic patients in Spain that culminated as *Alergológica*-92 [1]. In 2005, our Society repeated this observational, prospective, and cross-sectional study on a sample of 4991 subjects seen in allergic clinics and selected at their first interview. This trial, named *Alergológica*-2005, was carried out by allergists of every part of Spain over two selected periods of 2005 [2].

There are some infrequent and diverse diseases that occupy an important part of the time in the job of the allergists. These diseases were also evaluated in both surveys, and they were categorized as "Other allergic diseases" or "Other non-allergic diseases" depending on their etiologies.

The aim of this article is to analyze the prevalence of both groups of miscellaneous clinical entities, with or without allergic etiology; and also, to study the influence of several risk factors in their development. We sought to compare the current findings with the data obtained more than ten years before [1, 2].

Material and Methods

A randomized sampling study was carried out which extended over a year with two recruitment periods: March-June 2005 and September-December 2005. These periods were chosen as they were periods in which an increased incidence of allergic diseases was expected.

The analysis strategy was based on the estimation of prevalence for different allergic diseases. Data on the method employed in the survey are described elsewhere [3]. Essentially, the eligibility criteria were patients of both sex of any age who were treated for the first time in an allergic clinic, public or private, in Spain. All patients gave informed consent to participate in the study. The study was conducted by allergists and pediatricians. The questionnaire used for the interview contained questions regarding demographic characteristics, medical history and allergy history. Focusing on several infrequent or unspecific diseases seen by allergists, the pathologies were classified as described below:

- **Other allergic diseases (OAD).** The diseases included in this group were: vasculitis, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, pulmonary eosinophilia, drug-induced pulmonary infiltrates, idiopathic anaphylaxis, immunodeficiency, allergic gastrointestinal diseases, allergic urological diseases, unaffiliated cough, urticaria pigmentosa, nodosus erythema, gastroallergic anisakiasis and eosinophilic bronchitis.

- **Other non-allergic diseases (ONAD).** The diseases included in this group were: upper airways obstruction, cystic fibrosis, respiratory infection, deficits of alpha-1 anti-

Table 1. Patient Characteristics*

| | OAD | ONAD |
|-----------------------------|-----------------------------|----------------------------|
| Patients | 45 | 290 |
| Mean Age \pm SD (range) | 39.36 \pm 21.26 (1-82) | 35.13 \pm 22.2 (1-82) |
| Children | 8 (18%) | 73 (26%) |
| Sex | | |
| Male | 44% | 26.4% |
| Female | 56% | 63.6% |
| Smoking | | |
| Non smoker | 59.1% | 70.5% |
| Ex-smoker | 22.7% | 11.2% |
| Smoker | 18.2 | 10.3% |
| Race | | |
| Caucasian | 45 (100%) | 278 |
| Latin-American | - | 9 |
| Moroccan | - | 1 |
| Others | | 2 |
| Atopy | | |
| Family | 2.2-15% | 0.7-24.5% |
| Personal | 4.4-15.6% | 0.7-15.5% |
| Environment | | |
| Urban | 71% | 61% |
| Rural | 17% | 22% |
| Semi-urban | 12% | 17% |
| Housing | | |
| Flat | 74.4% | 70% |
| House | 25.6% | 30% |
| Mean Size (m ²) | 116.28 (45-300) | 112.7 (30-500) |
| Mean Persons | 3.5 (1-5) | 3.5 (1-21) |
| Age of house | | |
| < 10 years | 32% | 26.2% |
| 11-25 years | 25% | 33.2% |
| > 25 years | 43% | 40.6% |
| Animals at home | 44% | 37% |
| School area | | |
| Urban | 80% | 68% |
| Rural/semi-urban | 20% | 32% |
| Working area | | |
| Light Manual | 35% | 28% |
| Hard Manual | 11% | 16% |
| Sedentary | 27% | 27% |
| None | 27% | 28% |
| Economy | | |
| High | 6.8% | 2.3% |
| Medium/High | 40.9% | 42.2% |
| Medium/Low | 50% | 48.7% |
| Low | 2.3% | 6.8% |

Abbreviations: * All percentages refer to patients.

OAD indicates other allergic diseases and ONAD indicates other non-allergic diseases.

SD: Standard Deviation.

trypsin, bronchial obstructions, pulmonary embolism, cardiac insufficiency, parasitism, pulmonary malformations, otitis media, iritis, immotile cilia syndrome, pemphigus, gluten hypersensitivity and other diseases.

Results

A total of 4991 patients were studied. In OAD group, 45 patients were included, whereas in ONAD group, 290 patients were included. Demographic findings of both groups of patients, OAD and ONAD, are shown in Table I.

Allergic assistance received

The patients in the OAD group waited between 0 and 365 days to be seen by the allergist. The median value of the delay was 18 days. The patients from the ONAD group waited up

to 800 days to be seen by the allergist. The median value of that delay was 26 days.

In the OAD group, 73.3% (33 patients) visited a general practitioner a mean of 2.7 ± 3.2 times in the previous three months; while 31% (14 patients) visited the Emergency Room a mean of 2.3 ± 2.3 times in the preceding year and 35.6% (16 patients) had to be seen by another specialist a mean of 1.7 ± 1.09 times in the previous year. Three patients required hospital admission; one for 3 days, and another for 32 days. A total of 80 days of work were lost.

In the ONAD group, 62% (180 patients) visited general practitioner a mean of 2.7 ± 2.7 times in the previous three months, while 26% (75 patients) visited the Emergency Room a mean of 1.9 ± 1.7 times in the preceding year and 34% (98 patients) had to be seen by another specialist a mean of 1.8 ± 1.4 times in the previous year. Nine patients had to be admitted to hospital for 3 to 15 days.

In Table 2 other items of allergic assistance are shown.

Table 2. Data on Allergic Assistance Received*

| | OAD | ONAD |
|----------------------------------|--------------------------|---------------------------|
| Allergic assistance | | |
| Public hospital | 42.2% | 23.4% |
| Outpatient clinic | 28.9% | 38.6% |
| Private consultation | 22.2% | 24.5% |
| Not recorded | 6.7% | 13.5% |
| Referrals | | |
| Patient | 11.4% | 17.6% |
| Family practitioner | 63.6% | 47% |
| Specialist | 25% | 34.8% |
| | (11 patients) | (102 patients) |
| Internal medicine | 2 | 6 |
| ENT specialist | 2 | 21 |
| Pediatrician | 3 | 34 |
| Dermatologist | – | 5 |
| Pneumologist | – | 14 |
| Gastroenterologist | – | 3 |
| Dentist | – | 3 |
| Anesthetist | – | 2 |
| Intensive Care Unit | 1 | 1 |
| Hematologist | – | 1 |
| Oncologist | – | 1 |
| Emergency room | 2 | 2 |
| Other | 1 | 9 |
| Time on waiting list | 37.26 ± 64.5 days | 62.35 ± 112.2 days |
| Previous anti-allergic treatment | 64% | 51% |
| State of disease | | |
| Acute | 27% | 31.7% |
| Stabilized | 38% | 38.5% |
| Remission | 35% | 29.8% |
| Timing of disease | | |
| First episode | 33.6% | 35.7% |
| Reactivation | 63.4% | 64.3% |

Abbreviations: * All percentages refer to patients. OAD indicates other allergic diseases and ONAD indicates other non-allergic diseases.

Symptoms

The symptoms that motivated the allergy study are described in Table 3. In the OAD group, the reactivations of the disease were seasonal in 12% of patients, perennial in 44% and intermittent in another 44% of patients. In the ONAD group, the reactivations of the disease were seasonal in 13.6% patients, perennial in 51.8% and intermittent in 34.6% of patients.

Table 3. Patient Symptoms*

| Symptoms | OAD | ONAD | Total in Alergológica 2005 |
|-----------------|-------|-------|----------------------------------|
| Nasal | 17.8% | 29% | 52.3% |
| Ocular | 8.9% | 9.7% | 34.8% |
| Ear symptoms | 2.2% | 2.8% | 3.4% |
| Throat symptoms | 15.6% | 11.4% | 8.3% |
| Cough | 28.9% | 33.1% | 24.7% |
| Dyspnea | 15.6% | 15.5% | 24.5% |
| Wheezing | 6.7% | 11.7% | 16.1% |
| Food reaction | 20% | 4.8% | 6.1% |
| Drug reaction | 8.9% | 13.8% | 15.2% |
| Eosinophilia | 2.2% | 0.7% | 0.4% |
| Digestive | 13.3% | 29% | 1.3% |
| Skin symptoms | 35.6% | 5.2% | 20.4% |
| Latex reaction | 4.4% | 25.5% | 0.7% |
| Anaphylaxis | 15.6% | 0.7% | 1.4% |
| Other | 6.7% | 1% | 5.4% |

Abbreviations: * All percentages refer to patients. OAD indicates other allergic diseases and ONAD indicates other non-allergic diseases.

Definitive diagnosis

The definitive diagnosis in both groups of patients is shown in Table 4. The wide range of diagnoses is notorious. In both groups, indefinite diagnoses are at the top of the list. In OAD, the significant diagnoses were gastroallergic anisakiasis (10 patients), idiopathic anaphylaxis (7 patients),

Table 4. Definitive Diagnoses*

| Other Allergic Diseases (OAD) | Patients (n) | OAD and ONAD Combined (%) |
|---|--------------|---------------------------|
| Hypersensitivity pneumonitis | 2 | 0.6% |
| Idiopathic anaphylaxis | 7 | 2.1% |
| Immunodeficiency | 1 | 0.3% |
| Allergic gastrointestinal diseases | 1 | 0.3% |
| Cough of unknown origin | 17 | 5.1% |
| Gastro-allergic anisakiasis | 10 | 3.0% |
| Other diseases | 23 | 6.9% |
| Other Non-Allergic Diseases (ONAD) | | |
| Upper airways obstruction | 36 | 10.7% |
| Respiratory infection | 61 | 18.2% |
| Cardiac insufficiency | 3 | 0.9% |
| Parasitism | 3 | 0.9% |
| Otitis media | 4 | 1.2% |
| Iritis | 1 | 0.3% |
| Gluten hypersensitivity | 2 | 0.6% |
| Other diseases | 188 | 56.1% |

* All percentages refer to patients.

and hypersensitivity pneumonitis (2 patients). In the ONAD group, non allergic respiratory related diseases are the most frequent diagnoses.

The time spent in confirming the final diagnosis, considering both groups together, ranged between 1 and 210 days, with a mean time of 14.2 ± 25.5 days. However, the median value was only 1 day. The main diagnostic methods employed were: clinical history and physical examination in 86% of cases; skin prick tests in 73.7%; hematological and biochemical blood analysis in 28.7%, functional pulmonary tests in 20%, and radiological studies in 14.3%.

Quality of Life

Data on the OAD group are doubtfully relevant because only 14 patients were polled. Another 31 patients were lost. However, in these 14 persons, the findings showed a mean value of 47.4 ± 9.1 in the PCS-12 questionnaire, which is the physical version of SF12. Moreover, in the MCS-12 test, which is the psychological version of SF12, the mean value obtained was 45.2 ± 9.18 . In the ONAD group, 201 patients were lost, and 89 patients were polled. The findings showed a mean value of 43.9 ± 11.1 in the PCS-12 questionnaire and in the MCS-12 test the mean value obtained was 43.7 ± 12.67 .

Discussion

The aim of allergological health care is to provide allergic patients with those services best maintaining or restoring their health. One of the salient features of clinical practice is the enormous variability in actuation patterns, so that one and the same allergic condition is approached in varying manners by different physicians.

In the *Alergológica-92* survey, 76 patients belonged to the OAD group, while only 45 patients were counted in 2005 [1]. However, in the former survey, patients with an ONAD diagnosis were not polled [1]. The mean age of patients in the 2005 survey is higher. It was near 40 years versus 19 years in 1992 [1, 2]. It seems that allergological investigations are now claimed by people who are older than some years ago. There are also differences in sex, as in 2005 females predominated whereas in 1992, 54% of patients were male.

Data from *Alergológica-2005* revealed the presence of non-Caucasian persons. This fact shows the new make-up of Spanish society.

Most patients in *Alergológica-2005* and the ONAD group received their health care in outpatient clinics [2]. However, the OAD group was treated mainly in public hospitals. Moreover, in 1992 patients were predominantly referred by other medical specialists [1], but now most patients are referred by a family doctor, which shows the increase in the knowledge of general practitioners regarding allergy problems. Currently, pneumonologists and dermatologists continue to refer few patients to allergists in the OAD group. Paradoxically, the situation is different in the ONAD group.

Waiting lists in the OAD group in 2005 are lower than in 1992 [1]. Time on lists is also lower in both groups in 2005 than in the whole survey of this year. Nevertheless, in the 2005 survey, the patients referred for their first episode has increased, which again supports the idea of general practitioners having acquired a better knowledge of allergy-related matters. The quality of life perceived by patients in both groups is worse than obtained in the general population.

Unaffiliated cough is, as in 1992, the most frequent diagnosis. We can suppose that other medical specialists need to rule out the allergic etiology in these patients. Urticaria pigmentosa has disappeared; possibly because these patients are, at present, seen by dermatologists.

Whereas gastric anisakiasis has been known for several decades, the implications of *Anisakis simplex*-related allergic disorders had not been thoroughly studied until the late 1990s [4]. Data from the *Alergológica-2005* survey show the current knowledge of allergic disorders ascribed to *Anisakis simplex* contact [5-10]. Gastroallergic anisakiasis appeared as a differentiated disease in 10 patients in the OAD group. Allergic hypersensitivity symptoms in gastroallergic anisakiasis are clinical events accompanying a wide range of immunologic reactions as a host response against a ubiquitous parasite. Gastroallergic anisakiasis describes an acute hypersensitivity reaction emerging in the context of an acute parasitism by the nematode *Anisakis simplex* [6-9]. Other frequent allergic disorders and involvement of non-immunoglobulin E (IgE) mediated mechanisms are now being studied for a possible relationship with *Anisakis simplex* parasitism [10,11].

Idiopathic anaphylaxis was recorded in seven patients in the OAD group. Idiopathic anaphylaxis is a prednisone-responsive condition without external cause, but it can coexist with food-, medication-, or exercise-induced anaphylaxis. It consists of urticaria or angioedema associated with severe respiratory distress, syncope or hypotension, and gastrointestinal symptoms [12]. The data from 2005 are similar to the findings

of 1992. The frequency of this disease in our survey seems to be lower than previously reported [12, 13].

Hypersensitivity pneumonitis is a complex syndrome of varying intensity, clinical presentation, and natural history rather than a single, uniform disease [14]. It represents an immunologic reaction to an inhaled agent, particularly an organic antigen, occurring within the pulmonary parenchyma. Numerous triggering agents have been described, including, but not limited to, agricultural dusts, bio-aerosols, and certain reactive chemical species [14-18]. The prevalence and incidence of hypersensitivity pneumonitis appear to vary considerably depending upon case definitions, intensity of exposure to triggering antigens, season, geographical conditions, local practices and customs, proximity to certain industries, and host risk factors [14, 17-19]. The diagnosis of hypersensitivity pneumonitis was made in 2 patients of the total 4991 included in our study. The true incidence of this disease is considered unknown. In a population study the annual incidence of interstitial diseases was considered as 30:100000 inhabitants. Among these, hypersensitivity pneumonitis reached 2% of those 30 cases [18,19]. If we consider that the period of our study is not a complete year, the number of diagnoses of hypersensitivity pneumonitis made by Spanish allergists is suitably representative.

The amount of sheer number of entities that have no clear definition, affecting more than 60% of patients in both groups studied, is notorious. It is difficult to reach any valid conclusion about them. Process management is one of the management tools aiming at improving the efficiency, and the methodology of process management could allow a systematic analysis of the sequence of activities constituting those processes and of the professionals participating in them, with the purpose of reducing process variability [20].

A mean time of 14.2 ± 25.5 days was necessary to reach an accurate diagnosis. The time spent ranged from 1 to 210 days. However, most patients were diagnosed in 1 day. These findings can be explained by the varied nature of the diseases included in the two study groups in this article. In both groups, severe, moderate and mild pathologies coexisted.

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