

Increasing Incidence of Pediatric Eosinophilic Esophagitis in the Southwest of Madrid, Spain

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■ Abstract

Objectives: The incidence of eosinophilic esophagitis is unknown in our area. The aim of our study was to determine the incidence of eosinophilic esophagitis and its possible association with the most frequent absolute annual pollen counts.

Methods: A descriptive retrospective multicenter observational study was designed to calculate the incidence of eosinophilic esophagitis in children aged under 15 years in the southwest region of Madrid, Spain in 2002-2013 (data were provided by the Statistics Institute of Madrid). We collected data on age, sex, clinical presentation, and date of endoscopic diagnosis. Relative risk (RR) was estimated (Stata v.11) using negative binomial regression models to assess the association between incidence and pollen counts (provided by Subiza Clinic).

Results: The study population comprised 254 patients (192 male [75.6%], aged 0.5-14.99 years). The clinical presentation was esophageal impaction in 23.6%, dysphagia in 22%, gastroesophageal reflux-like symptoms in 44.9%, and other findings in 9.4%. The annual incidence from 2002 to 2013 per 100 000 children aged <15 years per year was, respectively, 0.81, 1.5, 0.37, 3.17, 3.07, 4.36, 6.87, 7.19, 8.38, 9.05, 9.14, and 9.68. The incidence of eosinophilic esophagitis increased by an average of 19% annually (RR, 1.19; 95%CI, 1.14-1.25; $P<.001$). In the overall analysis, the relationship between incidence and absolute annual and monthly counts during the pollen seasons of the respective pollen types was analyzed only for *Platanus* species, which had an RR >1 (1.17 and 1.06, respectively) ($P<.05$).

Conclusion: The incidence of diagnosis of pediatric eosinophilic esophagitis increased by an average of 19% annually. No significant association was found between incidence and pollen counts, except for a weak association with *Platanus* species.

Key words: Pollen. Eosinophilic esophagitis. Epidemiology.

■ Resumen

Objetivo: La incidencia de esofagitis eosinofílica es desconocida en nuestra área. El objetivo de nuestro estudio es determinar la incidencia de diagnóstico de esofagitis eosinofílica y su posible asociación con los recuentos absolutos anuales de los pólenes más frecuentes.

Métodos: Se diseñó un estudio descriptivo multicéntrico retrospectivo para el cálculo de la incidencia de esofagitis eosinofílica en niños menores de 15 años en el suroeste de la Comunidad de Madrid entre 2002-2013 (datos poblacionales obtenidos del Instituto de Estadística de la Comunidad de Madrid). Se recoge de cada paciente: edad, sexo, presentación clínica y fecha de diagnóstico endoscópico. Se estimó la asociación entre la incidencia y los recuentos polínicos (aportados por la Clínica Subiza) mediante cálculo del riesgo relativo usando modelos de regresión binomial negativa (Stata v.11).

Resultados: Se incluyeron 254 pacientes, 75,6% varones (n=192), de edades comprendidas entre 0,5-14,99 años. La presentación clínica fue: impactación esofágica 23,6%, disfagia 22%, síntomas sugerentes de reflujo gastroesofágico 44,9% y otros 9,4%. Las incidencias anuales desde 2002 a 2013 (nº casos/100.000 niños menores de 15 años/año) fueron respectivamente: 0,81; 1,5; 0,37; 3,17; 3,07; 4,36; 6,87; 7,19; 8,38; 9,05; 9,14 y 9,68. La incidencia de esofagitis eosinofílica se incrementó en una media anual de 19% (RR 1,19, 95% IC: 1,14-1,25, $p<0,001$). En nuestro estudio únicamente existió asociación (RR>1) entre la incidencia y los recuentos polínicos absolutos de *Platanus* spp anuales y durante los meses de máxima polinización (1,17 and 1,06, respectivamente) ($p<0,05$).

Conclusión: La incidencia de diagnóstico de esofagitis eosinofílica en la edad pediátrica se ha incrementado en una media anual de un 19%. No se encontró una asociación estadísticamente significativa entre la incidencia y los recuentos polínicos, excepto con el *Platanus* spp aunque ésta fue débil.

Palabras clave: Polen. Esofagitis eosinofílica. Epidemiología.

Introduction

Eosinophilic esophagitis (EoE) is a chronic local immune-mediated inflammatory process characterized clinically by symptoms suggestive of esophageal dysfunction and histologically by eosinophilic infiltration of the esophageal epithelium (>15 eosinophils per high-power field). The definition of EoE excludes other causes of esophageal eosinophilia, whether local or systemic [1]. In young children, typical symptoms are similar to those of gastroesophageal reflux disease (GERD), and, in older children, dysphagia and food impaction [2]. Treatment includes dietary restriction for certain foods, exclusively proton pump inhibitor (PPI) treatment, topical corticosteroids, and other treatments [3,4].

EoE is increasingly diagnosed in our setting [5]. In addition, the existence of a real increase in incidence, as reported in published epidemiological studies, is clear in other areas [6].

The incidence of EoE has been reported to be seasonal, although this has not been confirmed. Based on this factor and the pathogenic role attributed to food allergens, circulating aeroallergens may act as determinants of incidence and exacerbations through cross-reactivity [7,8]. However, this hypothesis remains controversial.

The objective of our study was to describe the incidence of EoE diagnosed in children under 15 years of age in the southwest of the region of Madrid, Spain between 2002 and 2013. The secondary objectives were to describe the clinical presentation pattern and to assess the relationship between the number of cases and the average level of circulating aeroallergens, both annually and in periods of peak pollen count.

Patients and Methods

We collected a retrospective sample of all patients under the age of 15 and newly diagnosed with EoE between 2002 and 2013 in 11 public hospitals in the southwest of the autonomous community of Madrid through review of electronic medical records. Cases were defined as patients with symptoms of esophageal dysfunction associated with the presence of esophageal eosinophilic infiltration ≥ 15 eosinophils per high-power field [1], including patients who responded to PPIs. Patients with other causes of EoE were excluded, as were those not belonging to the referral area or diagnosed with EoE before 2002. The variables collected from each patient were sex, month of endoscopic diagnosis, age, and diagnostic symptoms (esophageal impaction, dysphagia, gastroesophageal reflux-like symptoms, and other). The study was approved by the local ethics committee.

In order to assess clinical manifestations related to age of presentation, the total sample was divided into 2 groups consisting of patients aged <8 years and patients aged ≥ 8 years. In order to estimate the annual incidence, we used the referral population under 15 years of age for each hospital per year, as provided by the Statistics Institute of the region of Madrid (available at: <http://www.madrid.org/iestadis/>) (Table). This estimation was performed in the same way for each age group, taking the respective denominator in each case. The existence of statistically significant differences between the annual incidence by age group (patients <8 years and patients ≥ 8 years) was analyzed using the Mantel-Haenszel test.

A negative binomial regression model was used to estimate the possible association (relative risk [RR]) between EoE diagnosed in the pediatric population and the pollen counts.

Table. Population Under 15 Years and Absolute Pollen Counts

Year	No. of Cases	Population Under 15 Years of Age ^a			Absolute Pollen Counts, grains/m ³ of air ^b							
		Age <8 y	Age ≥ 8 y	Total	O	P	Po	C	Q	A	U	AA
2002	1	132 711	122 541	255 252	2605	7612	4985	9431	10 886	72	619	3271
2003	4	142 088	123 787	265 875	2452	5850	3773	4096	6430	48	584	1617
2004	1	150 220	122 957	273 177	801	3405	2612	6027	3005	58	476	1130
2005	9	160 060	123 857	283 917	3581	8354	1889	2906	10 956	47	322	1198
2006	9	170 119	123 407	293 526	2782	6471	5165	4456	5300	36	416	910
2007	13	174 431	123 906	298 337	2080	7738	6860	9499	7705	37	423	3087
2008	21	178 378	127 238	305 616	1211	10 289	4425	7296	7682	51	519	3123
2009	23	188 256	131 587	319 843	3628	7409	2560	4709	8455	20	503	1497
2010	39	272 220	193 351	465 571	2071	11 012	4176	4211	7399	50	385	2021
2011	43	276 494	198 628	475 122	3003	15 871	4120	12 875	10 982	84	574	2909
2012	44	277 020	204 568	481 588	1876	13 704	3487	4893	16 155	22	428	697
2013	47	274 301	211 054	485 355	5502	7149	5698	7252	6201	69	561	929

Abbreviations: O, *Olea*; P, *Platanus*; Po, *Poaceae*; C, *Cupressaceae*; Q, *Quercus*; A, *Artemisia*; U, *Urticaceae*; AA, *Alternaria alternata*.

^aInstitute of Statistics of the Madrid region.

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The average annual absolute pollen counts of the main taxons in Madrid (*Olea* species, *Platanus* species, *Poaceae*, *Artemisia* species, *Urticaceae*, *Cupressaceae*, and *Quercus* species) were provided by the Subiza Clinic (available at: <https://www.clinicasubiza.com>). The analysis included counts of *Alternaria alternata* fungus, as this is the main allergic outdoor fungus and is present throughout the year (Table).

The diagnostic period was represented as an indicator variable in groups of 1 year. From these data, the RR of being diagnosed with EoE was estimated based on the pollen levels using negative binomial regression models [9].

The same calculation with the absolute maximum pollen counts in each pollination period (obtained from Public Health Technical Paper No. 70: "Atmospheric Pollen in Madrid", which is available for consultation at <https://www.madrid.org/polen>), taking into account the incidence of cases in each period included. All calculations were performed using the statistical program Stata v.11. This study follows the principles for observational studies outlined in the Declaration of Helsinki.

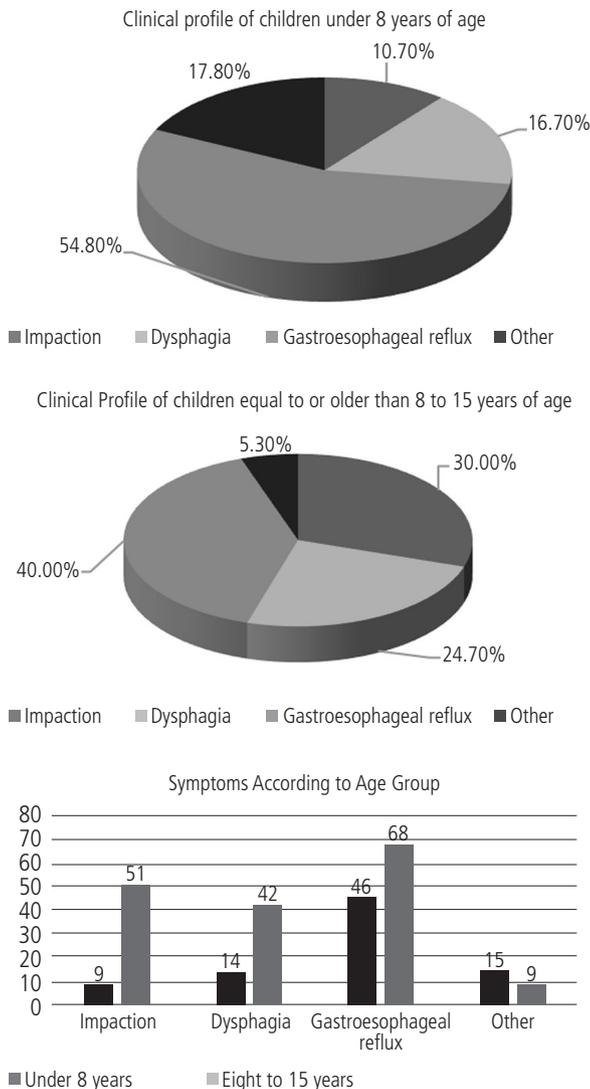


Figure 1. Clinical profile by age group.

Results

The study population comprised 254 patients (192 males [75.6%]). Mean (SD) age was 9.24 (3.43) years (median [IQR], 9.67 [0.5-14.99]); mode, 6.6 years). Eighty-four patients were under 8 years, and 170 were 8 years to 15 years old. The clinical presentation was as follows: esophageal impaction, 23.6% (n=60); dysphagia, 22% (n=56); gastroesophageal reflux-like symptoms, 44.9% (n=114); casual findings, 5.1% (n=13); and other findings (evaluated owing to low weight, diarrhea, *Helicobacter pylori* infection), 4.3% (n=11). Clinical presentation according to age group (<8 years and ≥8 years) is presented in Figure 1. Statistically significant differences were found between the groups ($P<.05$).

The overall mean incidence of EoE was 6.04/100 000 children <15 years of age per year. Incidence was 3.50 in patients aged <8 years and 9.41 in those aged 8 years to 15 years. This difference was statistically significant (RR, 2.68; 95%CI, 2.09-3.45; $P<.001$).

The annual incidence from 2002 to 2013 was, respectively, 0.39, 1.5, 0.37, 3.17, 3.07, 4.36, 6.87, 7.19, 8.38, 9.05, 9.14, and 9.68 cases/100 000 habitants aged <15 years/year. This upward trend is presented in overall terms and by age groups in Figure 2. It was estimated that, from 2002 to 2013, the incidence of EoE increased by an average of 19% annually (RR, 1.19; 95%CI, 1.14-1.25; $P<.001$).

The overall analysis of the relationship between the incidence and the absolute pollen counts, both annually and monthly during the peak pollen count period (pollen season), only revealed a statistically significant association ($P<.05$) with *Platanus* species, both annually and in the pollen season. However, the strength of this association was weak (RR, 1.06 and 1.10, respectively). According to this model, a 6% and 10% increase in the risk of developing EoE is expected for every 1000-unit increase in *Platanus* pollen counts annually and monthly during the pollen season, respectively. There was no association with other pollen counts ($P>.05$).

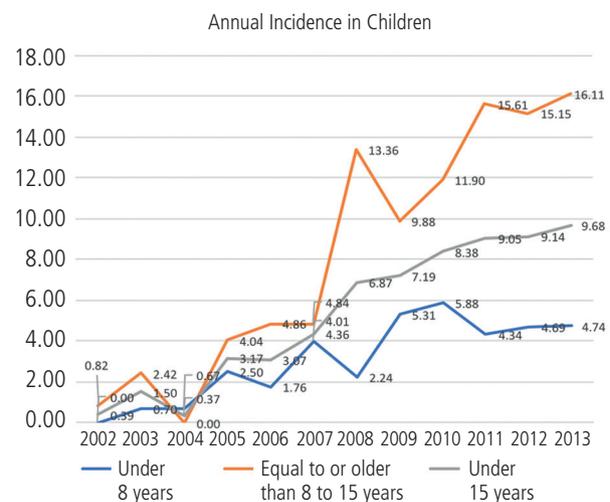


Figure 2. Annual incidence (number of cases/100 000 persons/year) both overall and by age group.

Discussion

The incidence of pediatric EoE in our area has increased in recent years by an average of 19% annually and in 2013 stood at 9.7/100 000 children/year. These results corroborate published data, although the incidence varies widely according to the geographical area. The systematic review by Soon et al [10] published in 2013 found incidences ranging from 1.6/100 000 persons/year in Denmark to 10/100 000 persons/year in the USA, with an average annual increase of 12%-17% [10]. A recent systematic review of 2016 by Arias et al [6] supports these results, finding a global incidence in children of 5.1/100 000 persons/year (lower than in adults), with a significant increase in diagnosed disease in studies carried out from 2008. Geographical variations similar to those described by Soon et al were observed, with significant differences between the United States (5.4/100 000 persons/year [95%CI, 1.6-11.5]) and Europe (1.7/100 000 persons/year [95%CI, 1.0-2.7]) [6]. These values come mostly from retrospective studies.

Pediatric EoE series are scarce in Spain. A retrospective series from a hospital in Barcelona published in 2005 presented 11 newly diagnosed patients in the period running from January 1997 to November 2003, although no actual incidence data were reported [5]. Another series was from a prospective observational study that included 17 patients with a diagnosis of EoE (>20 eosinophils per high-power field) in a hospital in Madrid from 2001 to 2009 [11]. Nevertheless, there are no reported data in Spain on incidence in children, and, to our knowledge, ours is the first study to provide data on the incidence of diagnosis of EoE in pediatric patients. We observed a clear increase in incidence during 2008-2009. This could be related to an increase in the number of endoscopies performed in the pediatric population, an active search for cases with greater diagnostic suspicion, and a real increase in the incidence of the disease.

In addition, some studies suggest that oral immunotherapy with food may also contribute to the increasing incidence of EoE, although we found no evidence for this possibility in our series [12].

Prospective series published in nearby regions include a mixed series of adults and children (age range, 6-63 years; mean age, 33.6 years) from 43 patients between 2006 and 2011 [13] and another pediatric series (<16 years) of 35 patients from January 2011 to December 2015, with a mean age of 9.6 years (4-16 years) [14]. Given that the reference population is not included in any of them, it is impossible to calculate the incidence. On the other hand, our incidence data are similar to those of an adult population reported by Molina et al [15] in Spain during 2007-2016 that also included PPI responder cases [15].

The prevalence of males and mean age at diagnosis coincide with findings in other publications [10].

Clinical presentation is similar to that reported elsewhere [16] and, as described above, there is a variation in the clinical presentation according to age group [17], with more frequent occurrence as atypical gastroesophageal reflux-like symptoms that do not respond to usual treatment in patients aged <8 years and as dysphagia/impaction in patients aged

>8 years [10]. Statistically significant differences were found for annual incidence according to age group. The incidence in the younger group may actually be lower or underestimated because of unspecified symptoms. The time of onset of the histological abnormality is unknown, as is that of symptoms.

The relationship between EoE and aeroallergens is controversial. A recent systematic review found no significant variations in the seasonal distribution of the incidence of the disease [18]. However, seasonality and pollination are not a purely temporally static concept, but are conditioned by climatic changes (eg, rain patterns) or type of vegetation, which are variable. Thus, studies such as that of Moawad et al [7] and Fahey et al [8] show that there may be a correlation between the incidence of EoE and some aeroallergens, although to date it has been impossible to distinguish which ones may be responsible. A recent systematic review recognizes that seasonal, geographical, and climate-based differences in disease prevalence could be due to multiple environmental exposures, although the exact mediators of this process remain elusive [19].

In our study, we found no statistically significant association with any pollen type except for *Platanus* species, both annually and monthly during the peak period, although the strength of the association was weak. According to this model, we could assume that for every 1000-unit increase in this particle, a 10% increase in the risk of EoE is expected in persons aged <15 years. A study of the period 1979-1993 in Madrid found *Platanus* species to be the second most frequent pollen in this area [20]. The high degree of awareness of this pollen means that it is a major cause of hay fever in the Madrid area [21]. The theory of cross-reactivity between aeroallergens and food allergens [22,23] might explain its relationship with EoE. Thus, massive inhalation in high amounts would exceed mucociliary clearance and enable pollen to reach the esophagus. In a situation of increased mucosal permeability, the immunological relationship in deeper layers and the recruitment of eosinophils could be triggered [24]. The degree of contamination and suspended particles in inhaled air could act as a booster [25,26].

The limitations of our study are partly a reflection of its retrospective nature. Incidence is probably underestimated because we excluded patients who were not included in the retrospective review and others from the catchment area who were diagnosed in other private or public centers. Therefore, our data reflect a minimal incidence of diagnosis. On the other hand, since we have no data about sensitization to *Platanus* species and other aeroallergens in these patients, we cannot establish a possible relationship. We did not evaluate the modifying effect of other environmental factors (eg, pollutants) on this association.

Given the retrospective nature of our study, the time of onset of symptoms was not accurately recorded. Onset of symptoms might more accurately express the onset of the disease, thus reducing the time to diagnosis. However, it is known that the disease can be detected as an incidental finding in endoscopies performed for other reasons, that the symptoms may be intermittent, and that inflammation may precede symptoms at onset [27]. Therefore, it is not possible to analyze whether the onset of symptoms is influenced or not by pollen counts.

Pollen counts were monitored in the center of Madrid. Although the origin of the data of absolute pollen counts reflects the variations of absolute pollen counts during each year, the pollen count could be different at various points in the same area, as it depends on the local vegetation.

In conclusion, our study is the first of its kind to provide data on the incidence of EoE in a pediatric population residing in an area of Madrid and demonstrates the real increase in this diagnosis over a 12-year period. We observed a weak association between the incidence and annual pollen counts of *Platanus* species. Well-designed prospective studies are needed to confirm these findings and should account for other factors such as environmental contamination.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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