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Pediatric eosinophilic esophagitis in Portugal

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Summary

Eosinophilic esophagitis (EoE) is an increasingly frequent diagnosis in our clinical practice, mainly in pediatric age. Allergic responses to food and aeroallergens have been increasingly implicated in the etiology of this disease. We describe a retrospective data analysis of pediatric EoE patients followed in our Immunoallergology Department.

Of the 25 children (22 male, average 10.8 years), 88% had prior history of rhinoconjunctivitis, 76% asthma, 48% eczema and 36% food allergy. After evaluation, we identified in 76% and 92% of patients food and aeroallergen sensitization, respectively; 68% had simultaneously food and inhalant sensitization and 96% had at least one positive test to aeroallergens or food allergens. The first (44%) and the most frequent (56%) symptom was dysphagia. The time between symptoms onset and the EoE diagnosis averaged 18.6 ± 29.4 months. A multidisciplinary approach is needed for a correct evaluation, intervention and follow-up of these patients.

Introduction

Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated inflammatory disease of the esophagus, characterized simultaneously by clinical symptoms related to oesophageal dysfunction and histological eosinophil-predominant inflammation and infiltration of the oesophageal epithelium (1).

First described in 1978 by Landres et al (2) and initially thought to be rare, it has taken a dramatic shift in prevalence over the past decades. Its rapidly increasing incidence has been shown in Europe and the USA and has recently been reported throughout the world (3-11).

Currently, studies in Western Countries point to a prevalence of 43 to 55 patients per 100,000 inhabitants, making it the second leading cause of chronic oesophagitis, after gastro-esophageal reflux disease (GERD) and the most frequent cause of dysphagia in young patients (12). In fact, between 5% and 15% of patients undergoing endoscopic evaluation for dysphagia will be diagnosed as having EoE and more than 50% of patients presenting in an emergency room with food impaction are now diagnosed with EoE (9,12-16).

In terms of pathophysiology, EoE is believed to be an immune-mediated allergic process of an unknown etiology. In fact, given the dramatic epidemiologic shift regarding EoE, allergen exposure has been postulated to play a role; a hypothesis compatible with it being a predominantly T helper-2 (Th2) lymphocyte driven disorder, with an increase in mucosal eosinophils, mast cells and basophils. Additionally, the basal cell proliferation found in these patients, with subepithelial remodeling and deposition of collagen, may contribute to the esophageal dysmotility found in EoE patients; explaining why the development of peristaltic dysfunction felt as dysphagia may occur so early in the disease course (17-29).

A growing number of papers show not only that patients with EoE have high frequencies of previous atopic eczema, food and

respiratory allergies, but also high frequencies of sensitization to food and aeroallergens (30-35).

Material and methods

We performed a retrospective analysis of patient's files who were evaluated at the Food Allergy Consultation in our Immunoallergology Department from February 2009 to March 2014, and who had received the EoE diagnosis according to the 2011 consensus guidelines (1). Additional inclusion criteria were: all patients were under 18 years of age, all were symptomatic at the initial evaluation at their first Food Allergy Consultation and all had performed diagnostic esophageal endoscopy with biopsy. A total of 25 patients fulfilled the criteria.

Patients were subsequently characterized according to: demographic data; prior history of allergic disease; clinical, laboratorial (peripheral eosinophilia and total IgE), endoscopic and histological features; sensitization profile (specific IgE, skin prick tests, prick-prick tests and patch tests) and evolution throughout their follow-up.

All patients were submitted to skin prick tests (SPT) with commercial extracts (Bial-Aristegui®, Bilbao, Spain) of inhalant (*Dermatophagoides pteronyssinus, Dermatophagoides farinae, Acarus siro, Blomia tropicalis, Euroglyphus maynei, Glycyphagus domesticus, Lepidoglyphus destructor, Tyrophagus putrescentiae,* dog fur, cat fur, feathers, *Aspergillus fumigatus, Alternaria alternata, Cladosporium herbarum, Cynodon dactylon, Gramineae* mix, *Phleum pratense*, *Olea europaea, Artemisia vulgaris, Platanus, Plantago*) and food allergens (*Pho d 2, Pru p 3*, shrimp, tropomyosin, cow's milk, α-*lactoalbumin*, β-*lactoalbumin*, *casein*, egg yolk, egg white, ovomucoid, ovalbumin, wheat, soy, peanut, walnut, hazelnut, almond, pistachio, cashew, porc, beef, turkey, hake, cod). Additional extracts for food allergens were used, when there was a high clinical suspicion (based on the individual clinical history) of an additional possible food sensitization.

Prick-prick tests were performed for all negative food allergens on the SPT battery, and to the foods to which there was a high clinical suspicion of being a possible culprit.

Specific IgE was performed for all the food allergens investigated on the SPT battery and the prick-prick tests.

Patch tests were performed using a whole food sample on the patients back. The patches were left in place for 48 hours, after then they were removed and an initial reading was taken one hour later. The final reading was taken a further 48 hours later.

All EoE patients performed a standard patch test battery with native food (milk, egg yolk and white (raw and cooked), wheat, corn, peanut, walnut, cashew, pistachio, hazelnut, pinion, cooked beef, cooked chicken, cooked porc, cooked turkey, cooked shrimp, cooked cod, soy). Also additional patch tests were performed for foods to which there was a high clinical suspicion based on each clinical history.

IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. was used for statistical analyses of the data: relative frequencies, averages, standard deviation, mediums and binomial tests were performed.

Results

25 patients with EoE diagnosis in pediatric age were included in this study. Their characteristics and correspondent statistical analyses appear in **table 1** and **figure 1**.

Figure 1 *- Comparison of EoE symptoms by patient age. Green bar: children up to 6 years, yellow bar: children 6-12 years, and blue bar: children 12-18 years of age.*

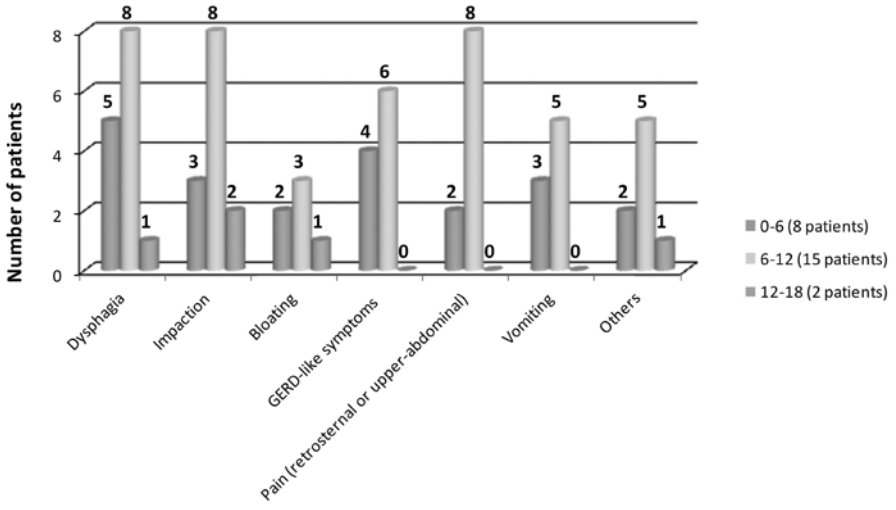

Table 1 *- Characterization of the pediatric population and statistical analyses of its binomial variables.*

Binomial variable		**Positive test in children**	
		Number of patients (%)	**p-value (binomial test)**
Male gender		22 (88)	**< 0.01**
Atopy prior to EoEd	Food allergy	9 (36)	NS
	Eczema	12 (48)	NS
	Asthma	19 (76)	**< 0.01**
	Rhinoconjunctivitis	22 (88)	**< 0.01**
	At least 1 of the 4 previous	24 (96)	**< 0.01**
First symptom	Dysphagia	11 (44)	NS
	GERD-like symptoms	4 (16)	NS
	Vomiting	3 (12)	NS
	Bloating	3 (12)	NS
	Impaction	2 (8)	NS
	Pain (retrosternal or upper-abdominal)	1 (4)	NS
Symptoms	Dysphagia	14 (56)	NS
	Impaction	13 (52)	NS
	GERD-like symptoms	10 (40)	NS
	Pain (retrosternal or upper-abdominal)	10 (40)	NS
	Vomiting	8 (32)	NS
	Others (anorexia, lower abdominal pain, chocking, food refusal)	8 (32)	NS
	Bloating	6 (24)	**< 0.01**
Positive Specific IgE	Mites	17 (68)	NS
	Food	16 (64)	NS
	Pollens	13 (52)	NS
	Animal epitheliums	7 (28)	**< 0.01**
	Fungi	3 (12)	**< 0.01**
Positive SPT and prick-prick test	Mites	19 (76)	**< 0.01**
	Food	16 (64)	NS
	Milk	8 (32)	NS
	Shellfish	7 (28)	**< 0.01**
	Egg	5 (20)	**< 0.01**
	Cereal	4 (16)	**< 0.01**
	Nuts	4 (16)	**< 0.01**
	Fish	3 (12)	**< 0.01**
	Meat	3 (12)	**< 0.01**
	Fruits	2 (8)	**< 0.01**
	Soy	0 (0)	**< 0.01**
	Pollens	14 (56)	NS
	Animal epitheliums	8 (32)	NS
	Fungi	6 (24)	**< 0.01**

Binomial variable		Positive test in children	
		Number of patients (%)	p-value (binomial test)
Positive patch test	Shellfish	12 (48)	NS
	Meat	6 (24)	**< 0.01**
	Egg	4 (16)	**< 0.01**
	Cereal	3 (12)	**< 0.01**
	Nuts	2 (8)	**< 0.01**
	Fish	2 (8)	**< 0.01**
	Cephalopods	1 (4)	**< 0.01**
	Soy	0 (0)	**< 0.01**
Endoscopy findings	Normal	1 (4)	**< 0.01**
	Furrows	20 (80)	**< 0.01**
	White plaques	10 (40)	NS
	Narrowing	8 (32)	NS
	Erosive esophagitis	7 (28)	**< 0.01**
	Rings	4 (16)	**< 0.01**
	Stricture	0 (0)	**< 0.01**
Histology findings	15-40 eos / HPF (PEC)	18 (72)	**< 0.01**
	> 40 eos / HPF (PEC)	7 (28)	**< 0.01**
	Microabscesses	8 (32)	NS
Food sensitization		19 (76)	**< 0.01**
Aeroallergens sensitization		23 (92)	**< 0.01**
Food and/or Aeroallergen sensitization		24 (96)	**< 0.01**

SPT - Skin prick test, Eos - eosinophils, HPF - High power field, PEC - peak eosinophil count, NS - not significant p-value ($p > 0.01$)

22 (88%) were male, with a statistical significant preponderance for the male gender ($p < 0.001$). The minimum age, at the time of this study, was 4 years old and the maximum 16, with an average age of 10.8 ± 3.4 years and a median of 11 years.

The average age at EoE diagnosis was 6.8 ± 3.6 years (91 ± 45.9 months), ranging from 1 year (13 months) to 14 years (171 months). EoE diagnosis was always confirmed after oesophageal biopsy, which was performed within three months prior or after the first Food Allergy Consultation. Diagnosis was reached prior to the Food Allergy Consultation when patients were first referred to a Pediatric Gastroenterology Consultation, performed the biopsy, and then were referred the Food Allergy Consultation. Diagnosis was reached after the Food Allergy Consultation when patients were first referred to a Food Allergy Consultation and then, referred to a Pediatric Gastroenterology Consultation to perform a oesophageal biopsy.

After diagnosis, the subjects had an average follow-up time at our Food Allergy Consultation of 25.5 ± 12.3 months, with the shortest follow-up time being 5 months and the longest 45 months.

The time elapsed between symptoms onset and the time of diagnosis averaged 18.6 ± 29.4 months, with a minimum time corresponding to 1 month and the maximum 133 months.

We searched for pre-existing allergic disease: 22 (88%) had prior history of allergic rhinoconjunctivitis ($p < 0.01$), 19 (76%) of asthma ($p < 0.01$), 12 (48%) of eczema and 9 (36%) had a history of food allergy (9 to milk, 2 to egg, 1 to fish and 1 to nuts). Overall, 96% had at least one prior atopic condition ($p < 0.01$).

Clinically, all patients had at least one symptom attributable to oesophageal dysfunction. The most prevalent were dysphagia in 14 (56%), food impaction in 13 (52%) patients, GERD-like symptoms in 10 (40%) and epigastric / retrosternal pain in 10 (40%). The most frequent onset symptom was dysphagia (44%).

Total IgE and peripheral eosinophil count were analyzed and a great variability was found. Total IgE averaged 621 ± 373 kU/L

(170-1830) and peripheral eosinophils averaged 532 ± 714 cells / mL with 3 patients having eosinophils count over 1000 cells/mL. The most frequent positive specific IgE were to mites (68%), food (64%) and pollens (52%).

Positive skin prick revealed sensitization to mites (76%), food (64%) and pollens (56%). Positive patch tests were positive to shellfish (48%), meat (24%), egg (16%) and cereal (12%).

Overall, in our pediatric population, 23 (92%) had at least one positive test to aeroallergens ($p < 0.01$), 19 (76%) had at least one positive test to food allergens ($p < 0.01$), 17 (68%) had at least one positive test to aeroallergens and simultaneously had at least one positive test to food allergens, and a total of 24 patients (96%) had at least one positive test to aeroallergens or food allergens ($p < 0.01$).

At EoE diagnosis, the most common endoscopic finding were furrows (80%) and white plaques (40%). The biopsies revealed in 7 (28%) patients > 40 eos/HPF and in 8 (32%) patients microabscesses.

The allergy tests were used to select the exclusion diet, and oral fluticasone (MDI in a dose of 250-500 mcg/day) was prescribed during a 6 month period. After six months, all patients repeated endoscopy and biopsies; after this time there was histological normalization in 8.3% of pediatric patients and clinical improvement in all of them.

Discussion

EoE is becoming a more frequent diagnosis. However, published EoE data from Portugal is still lacking. The closest available data comes from Spain and it may not be an exact match to the Portuguese population. There are differences in patient characteristics and clinical manifestations from reports from countries with similar diet and geographical location, as Spain (31,33,36), France (38) and Italy (39). One of the essential aspects of this study is the description of clinical and allergological characteristics of a Portuguese pediatric population with EoE.

Our study shows a statistically significant preponderance for the male sex with a M/F ratio of 7/1, a much higher ratio than that present in other studies (22,31,37,40-42), which indicate a 3/1 ratio. This difference may be explained by our small sample size. Nevertheless, the male gender seems to be highly associated with the development of EoE.

No conclusion could be found about the age of EoE diagnosis in our study, although most of our patients were diagnosed between the ages of 6 and 18 years of age; similar to other studies: 7.4 ± 3.8 years found by Rezende et al (30) or the 9 ± 3.8 years found by Lucendo et al (31). This age range may indicate that EoE is not a disease characteristic of toddlers, as it is of older children. This may be explained by an immature immune system in toddlers.

The time elapsed from symptom onset to diagnostic endoscopy, averaged 25.44 ± 12.30 months, with 23 patients (92%) being diagnosed between the ages of 6 and 18 years-old. Nonetheless, 48% were diagnosed within the first 6 months and 76% within the first 2 years of disease. This delay in diagnosis may be explained by the lack of awareness of this disease and the undervaluation of symptoms, especially in younger children with more unspecific symptoms. These results are in line with the average 28 months described by Lucendo et al (31) in Spain; but still far beyond the average of 3.9 months described by Sorser et al (43).

In line with previous studies, we have documented a high prevalence of pre-existing atopic diseases in our patients, with almost all (96%) having at least 1 prior atopic condition. This high prevalence is also found in other series, even though our population had a particularly high rate (**table 2**). As for food allergy prior to EoE diagnosis, the main allergen was milk; which is in consonance with the high prevalence of milk allergy in the pediatric age and might not be directly related with the posterior development of EoE.

The sensitization profile supports the numerous studies stating the high prevalence of allergic sensitization in EoE patients. Our patients showed a greater aeroallergen (91.7%) than food sensitization (75%). Whether the high prevalence is due to the high concomitant frequency of respiratory allergic diseases or is part of the pathophysiological process of EoE development, is a matter requiring further study.

Clinically, dysphagia was the most frequent symptom (56%), with impaction (52%) the second most frequent. It is important to point out the high number (32%) of pediatric patients who referred more unspecific symptoms (anorexia, lower abdominal pain, chocking, food refusal); which may indicate a difficulty for younger children to correctly explain and complain about what they are feeling, and which may delay the diagnosis in some cases (**table 2**). These findings highlight the importance of a thorough medical history, and the importance of inquiring the parents about coping mechanisms of children.

We have also found that many patients' parents confounded the results, pointing mainly to more exuberant symptoms, as vomiting or impaction. However, when questioned more thoroughly, it was possible for most of them to pin point previous undervalued symptoms of dysphagia (both by the parents and the children).

In this pediatric population, we found a high percentage of abnormal endoscopies, whose main abnormalities were furrows ($p < 0.01$) and white plaques. These alterations also seem to be fairly frequent in others studies (**table 2**), making it important to suspect and discard EoE when they are seen. Our results had a very small number of normal endoscopies (4%), albeit with disease, compared to other studies. But is never too much to underline the importance of excluding EoE simply on the basis of a normal endoscopy and the need for biopsies. Histologically, we found an

Table 2 - *Comparison of EoE characteristics between studies.*

	Current study (25 children)	**(30) (35 children)**	**(22) (381 children)**	**(43) (103 children)**	**(56) (30 children + adults)**	**(31) (705 children + adults)**	**(37) (43 children + adults)**
Rhinoconjunctivitis	88%	74.2%	X	57.4%	43.3%	47.4%	72%
Asthma	76%	60%	X	36.85	50%	32.8%	
Eczema	48%	42.8%	X		13.3%	6%	7%
Food allergy	36%		X	46%	X	25.7%	49%
At least 1 of the 4 previous	96%	X	53%	X	93.3%	61.8%	83.7%
Dysphagia	56%	28.5%	18.1%	X	X	54.9%[1]	19%
Impaction	52%	11.4%	X	X	X	26.3%[1]	9%
Bloating	24%	X	X	X	X	X	X
GERD-like symptoms	40%	X	X	X	X	7.4%[1]	X
Pain (retrosternal or upper-abdominal)	40%	28.5%	49.9%	X	X	15.8%	X
Vomiting	32%	71.4%	57.2%	X	X	24.6%[1]	X
Normal	4%	2.8%	32%	X	3.3%	27.9%	X
Stricture	0%	X	X	X	X	X	X
Furrows	80%	60%	41%	X	X	X	X
Rings	16%	22.8%	12%	X	X	50.6%	X
Narrowing	32%	X	X	X	X	X	X
Erosive esophagitis	28%	X	X	X	X	X	X
White plaques	40%	68.7%	15%	X	X	X	X
Food sensibilization present (specific IgE, prick, prick-prick or patch test)	76%	45.75	X	X	X	X	53.6%
Aeroallergens sensibilization present (specific IgE, prick or prick-prick)	92%	X	X	X	X	X	74.4%
Food and/or Aeroallergen sensibilization (specific IgE, prick, prick-prick or patch test)	96%	77.1%	X	X	X	X	X

[1]These results are for the children in this study alone, and not the 705 children and adult cohort.
X - value not present in the original articles.

unusually high number of microabscesse formation (32%) which may indicate a more exuberant or prolonged disease and which may explain why so many endoscopies were abnormal.

The allergic profile revealed a very high frequency aeroallergen (92%, $p < 0.01$) and food sensitization (76%, $p < 0.01$). These high numbers of aeroallergen sensitized patients suggest that these allergens may contribute to the etiology of this disease.

Another interesting finding was the high prevalence of positive patch tests. In the 2011 EoE guidelines, it was reviewed that 30 to 95% of patients may have a positive patch test. However, by far the most common positive test was to shellfish (48%). The meaning of this is still unclear and further studies are needed to determine the true prevalence of shellfish allergy in EoE patients. In our pediatric population, some of the children had never knowingly eaten shellfish but presented positive patch and/or prick tests. This could be due to a previous exposure to shellfish (accidental, due to cross-contamination or to hidden allergens in processed foods) (44,45). However, a different route has been proposed to account for this sensitization. In a 2003 study, a population of orthodox Jews with perennial allergic rhinitis and

dust mite hypersensitivity (and who are prohibited by religious dietary laws from eating shellfish), was found to have a positive sensitization to shrimp (46). The term "mite-crustaceans-molluscs syndrome" is sometimes used to describe clinically relevant cross-reactivity between crustacean and dust mites (47-50).
Considering this, when implementing the exclusion diet in these patients, exclusion of shellfish seemed beneficial. The authors suggested this approach to the patients for the following reasons: 1) a six-food elimination diet (which excludes shellfish from the patients diet) has shown to be effective in EoE both in adult and pediatric patients (51-53); 2) targeted dietary elimination therapy has also shown to be an effective option for in some patients with EoE (54) and given that shellfish sensitization had been shown in several of our patients, exclusion of shellfish in these patients was part of the targeted elimination diet; 3) recommendation to avoid specific foods and awareness of the importance of label reading might be helpful in preventing accidental exposures attributed to failure to read labels (a cause of accidental exposures in food-allergic patients) (55).
No positive patch tests were found for milk, suggesting that milk allergy in our EoE pediatric population seems to be exclusively mediated by IgE dependent mechanisms.

Conclusions

Dysphagia is not only the most frequent symptom, but also the most frequent first symptom in our patients.
Furrows and white plaques are the most frequent endoscopic findings and, when present, EoE should always be excluded. However, even in a normal esophagus, biopsies should be made as it does not exclude the presence of EoE.
There is still a considerable delay between symptom onset and EoE diagnosis, which given the high morbidity of this disorder highlights the need for further awareness and early diagnosis.
We confirmed the high prevalence (96%) of sensitization in pediatric EoE patients; with 92% with aeroallergen sensitization and 76% with food sensitization.
Patch tests seem to be an important part of the allergological evaluation, allowing for the identification of additional food sensitizations not detected by specific IgE, SPT or prick-prick tests. In our population, we found positive patch tests in 56% of the children, but further investigation is needed to understand the pathophysiological implications of this high frequency of food sensitization observed in patch tests.
A conjoined approach by different specialties to this disease is needed for a correct evaluation, intervention and follow-up of these patients.
This study gives important information about the characteristics of EoE pediatric patients in Portugal; nonetheless, further data is needed for a better understanding of this disease.

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