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G Hiremath
Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Baylor College of Medicine, Houston, TX

D Byramji
Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Baylor College of Medicine

A Pacheco
Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Baylor College of Medicine

G Constantine
Baylor College of Medicine

C Davis
Pediatric Allergy, Immunology and Rheumatology, Texas Children's Hospital, Baylor College of Medicine

See next page for additional authors

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Eosinophilic Esophagitis in Children and Its Relationship with Parental Allergies: Texas Children's Hospital Experience

Girish Hiremath[a], **Darius Byramji**[a], **Ann Pacheco**[a], **Greg Constantine**[b], **Carla Davis**[c], **Robert Shulman**[a,d], and **Anthony Olive**[a]

[a]Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Baylor College of Medicine

[b]Baylor College of Medicine

[c]Pediatric Allergy, Immunology and Rheumatology, Texas Children's Hospital, Baylor College of Medicine

[d]Children's Nutrition Research Center, Baylor College of Medicine

Abstract

Background—Eosinophilic esophagitis (EoE) is an allergen mediated, clinicopathological condition affecting all ages. The characteristics of children with EoE in the southwestern United States (U.S.) have not been fully described. Furthermore, very little is known about the relationship between parental allergies and risk of EoE in their offspring in this patient population.

Aims—To characterize children with EoE, and to examine the relationship between prevalence of parental allergies and occurrence of EoE in their offspring at a single referral pediatric center in southwestern U.S.

Methods—Demographic and clinical information of 126 children (≤ 18 years of age) with EoE was abstracted in a pre-determined data extraction form and analyzed. The allergy history was collected from biological parents of 61 children (parent-child cluster) with EoE in a standardized questionnaire and analyzed.

Results—The median age at presentation was 8 years (interquartile range: 4–13). The majority of our patients were male (71%) and Caucasian (59%). Overall, 84% of children reported allergies. Prevalence of food allergy was significantly higher compared to environmental allergies (P=0.001). At least 46% of parents reported allergies. A significantly higher proportion of fathers had developed allergies during their childhood compared to adulthood (P=0.03).

Conclusions—The characteristics of EoE in our patients were similar to those reported from other parts of the country. Childhood onset of paternal allergies appears to be a risk factor for occurrence of EoE in their offspring. Additional research to elucidate the relationship between parental allergies and occurrence of EoE in their offspring is warranted.

Corresponding author: Girish Hiremath, MD MPH, Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Baylor College of Medicine, Houston, TX 77030, girish.hiremath@gmail.com, Tel: 615-343-9034; Fax: 615-875-1742.

Keywords

Eosinophilic esophagitis; Epidemiology; Food allergy; Parent-Child cluster; Parental allergies

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune mediated condition characterized by intense eosinophilic inflammation of the esophagus i.e. presence of 15 or more eosinophils in the most severely involved high-powered field (eos/hpf), symptoms of esophageal dysfunction and failure to respond to adequate proton-pump inhibitor (PPI) therapy [1]. It is commonly associated with food allergies in affected individuals. With an estimated 18% increase in the prevalence of food allergies in the United States (U.S.) [2], the burden of EoE is expected to escalate in upcoming years. Yet the natural history of pediatric EoE remains to be fully understood.

While remarkable advances have been made in understanding certain aspects of EoE [3], much remains to be elucidated about the epidemiology of pediatric EoE. Epidemiologic descriptions have the potential to provide important etiologic clues about the natural history of EoE. Furthermore, recognizing geographic differences in pediatric EoE can provide important etiologic clues pertinent to specific patient population. There are few data on characteristics of EoE in children and on identifying at-risk children in order to ensure timely diagnosis of EoE to educate parents/caretakers about the potential of their offspring to develop EoE. One of the barriers in characterizing pediatric EoE in the U.S. is related to the difficulty in conducting epidemiological studies at the tertiary referral centers with wide catchment areas [4]. To our knowledge, the epidemiologic determinants of the pediatric EoE population in southwestern U.S. have not been adequately described.

Our institution represents a large, tertiary care referral center, serving the needs of the greater Houston area, Texas, adjoining U.S. states, and Central America. Moreover, the Houston area is one of the most ethnically diverse regions in the U.S. The Eosinophilic Gastrointestinal Disorders (EGID) Clinic at Texas Children's Hospital is one of the prominent centers in the southwestern U.S. The EGID Clinic offers a multidisciplinary approach to the evaluation and treatment of EGIDs, including the services of a gastroenterologist, allergist, dietitian, social worker and a clinical psychologist. A majority of children with EGIDs (including EoE) are referred to this clinic by the primary care physicians in the community, allergists and gastroenterologists for further evaluation and management. Therefore, our patient population offers a unique opportunity to examine the epidemiologic determinants of EoE in an ethnically diverse pediatric population in southwestern U.S. and allows us to address some of the critical gaps in the field.

In this study we sought to characterize EoE among children managed in the EGID clinic at Texas Children's Hospital and to examine the relationship between prevalence of parental allergies and occurrence of EoE in their offspring. Despite the diverse population mix served by our center, based on the existing literature we hypothesized that EoE would affect higher proportion of Caucasian children in our cohort. We also hypothesized that most of the parents of children with EoE would have one or more allergic condition(s) as has been

previously described in the context of other allergen-mediated conditions such as asthma and atopic dermatitis.

METHODS

Subjects

We reviewed the medical records of all children (under 18 years of age) receiving care in our multidisciplinary Eosinophilic Gastrointestinal Disorders (EGID) Clinic between June 2010 and June 2015 and diagnosed with EoE. Cases of EoE were defined per the 2011 updated consensus guidelines [1]. Specifically, children were required to have symptoms suggestive of esophageal dysfunction and persistent dense eosinophilic inflammation (>15 eos/hpf) while they were on recommended proton-pump inhibitor therapy and in the absence of other competing causes of esophageal eosinophilia such as gastroesophageal reflux disorder. Children diagnosed with other forms of eosinophilic intestinal disorders (e.g., eosinophilic gastroenteritis or eosinophilic colitis) or systemic eosinophilic disorders (e.g., hypereosinophilic syndrome) were excluded.

Data

Pertinent data abstracted included: demographics [such as age; gender; race (as reported by the patient or parent)]; clinical history [e.g., history and duration of other atopic disease such as allergic rhinitis/sinusitis, asthma, environmental and/or food allergy; exposure to concurrent medications], presenting symptoms (i.e., nausea, vomiting, failure to thrive, dysphagia, chest pain, abdominal pain); and the results of immediate hypersensitivity skin prick testing (SPT) for environmental (tree, grass, and weed pollen, dust mites, cat, dog, cockroach, mixed feathers, mold) and food allergens (cow's milk, egg, wheat, soybean, peanut, tree nut mix, codfish and shellfish mix-Greer®).

A.P. used a standardized data extraction form to gather relevant data from the medical records. D.B. and G.H. randomly checked the database for accuracy and consistency of the data.

Parental Allergy Information

To understand the relationship between allergies among biological parents and the occurrence of EoE in their offspring, we collected the allergy history of biological parents in a standardized clinic intake questionnaire. The biological parents accompanying their children diagnosed with EoE in our EGID clinic between August 2012 and June 2015 were invited to participate in this study. The questionnaire was designed to gather information on: (a) presence or absence of allergic conditions, (b) age at onset of allergies [as a child: ≤ 18 years or as an adult: > 18 years), and (c) allergic condition(s) experienced (e.g., eczema, asthma, allergic rhinitis, food allergies, environmental allergies, and EoE) during their lifetime. Non-biological or foster parent(s)/caretaker(s) were not included in this part of the study.

Statistical analysis

Descriptive statistics were used to characterize the demographic and clinical features of subjects and analyze the allergy information provided by the biological parents. Given the small size and/or non-normal distribution of continuous variables, the results are presented as median (interquartile range) (IQR) and also as mean ± standard deviation (SD). Wilcoxon rank-sum test and the Fisher exact test were used to compare continuous and categorical variables, respectively for statistical significance. The statistical significance was determined at $P < 0.05$. All analyses were performed on Stata 10.2 (StataCorp, College Station, TX).

Ethical considerations

The Institutional Review Board at the Baylor College of Medicine approved the retrospective review of medical records and the prospective questionnaire-based parent-child cluster study. Informed consent was obtained from parent(s) prior to collecting relevant allergy information.

RESULTS

The schematic study design is presented in Figure 1. In all, 183 patients visited the EGID clinic between June 2010 and June 2015. Of that, 126 (69%) patients had EoE. The medical records of all 126 children with confirmed EoE were reviewed to characterize EoE in our patient population (Table 1), and parental allergy history collected from 61 parent-child cluster was analyzed (Table 2).

Age and Gender

The median age [interquartile range (IQR)] age was 8 years (4 – 13) with a range from 7 months and 18 years. Ninety (71%) children were males. The median (IQR) age at presentation was similar in males and females [9 (5 – 13) vs. 9 (8 – 13); p=0.80].

Race and Ethnicity

The racial and ethnicity breakdown revealed that our cohort consisted primarily of Caucasians [n (%): 74 (59%)]. Other groups included: African American [18 (14%)], Hispanic [13 (10%)], Asian [4 (3%)] and others [9 (7%)]. The median age at presentation was comparable between all ethnic groups. EoE affected a higher proportion of males compared to females in each group. The results are summarized in Supplementary Table 1 and Supplementary Table 2, respectively.

Allergic co-morbidities and allergy testing

One hundred and six (84%) children had one or more co-existing allergic condition. Food allergies [74 (59%)], allergic rhinitis [57 (45%)], eczema [54 (43%)], and asthma [50 (40%)] were the most common associated allergic conditions. Sixty six (52%) children with EoE had skin prick test (SPT) for environmental and food allergies prior to initiating their care in our EGID clinic. A significantly higher proportion of them were male [male: 55 (71%) vs. female: 22 (29%); P=0.0007]. Forty children (61%) were reactive to all allergens and 28 (42%) were reactive to only one allergen.

Relationship between age of the child and the presenting symptoms

The majority of our patients presented with a combination of two or more symptoms, and Figure 2 shows trends of presenting symptoms and their relationships with age. Nausea and vomiting were the most common complaint and accounted for 68% of presenting symptoms. Other common presenting symptoms included abdominal pain (42%), heartburn or chest pain (33%), failure-to-thrive (33%), esophageal food impaction (24%). The younger children (between ages 3 to 5 years) commonly presented with nausea, vomiting and failure-to-thrive or poor weight gain and the school aged children (between ages 6 to 9 years) commonly presented with abdominal pain and heartburn. The teenagers and adolescents commonly presented with heartburn, difficulty in swallowing and esophageal food impaction.

Prevalence of Parental Allergies and EGIDs

Allergy information from biological parents of 61 children with confirmed EoE was collected and analyzed. The demographic characteristics (such as age, gender, ethnicity, allergic co-morbidities) of these 61 children were similar to that of our entire cohort and are summarized in Supplementary Table 3.

Eczema and asthma (54%) were the two most prevalent allergic conditions among mothers (56% and 54%, respectively) and fathers (38% and 36%, respectively). While the prevalence of eczema and asthma was higher in mothers compared to fathers, this difference did not attain statistical significance (P=0.18 and P=0.19). In all, parents of 13 (21%) children with EoE reported no allergic co-morbidities. Furthermore, we did not observe a statistically significant relationship between parental allergy profile and the gender of the child diagnosed with EoE. A relatively small number of parents [n=6 (10%)] of children with EoE reported being diagnosed with EGIDs [EoE=4 (67%), eosinophilic gastroenteritis=1 (17%), eosinophilic colitis=1 (17%)]. The results are summarized in Table 2.

Relationship between Parental Allergy and EoE in their Children

The results are summarized in Table 2. A significantly higher proportion of parents (mother or father) of children with EoE reported allergies compared to the proportion of parents (mother or father) not reporting any allergic conditions (79% vs. 21%; P=0.0002).

A significantly higher proportion of fathers of children with EoE reported having developed allergies during their childhood as opposed to fathers having developed allergies as adults [71% vs. 25%; P=0.03]. This difference was not seen among mothers. The allergy profile of mothers and fathers was comparable.

DISCUSSION

We examined the demographic and clinical determinants of children with EoE receiving care in our center, and also assessed the relationship between prevalence of parental allergies and occurrence of EoE in their offspring. Our observations indicate that among children living in our catchment area, EoE is more common in male Caucasians. These observations are consistent with other reports describing the epidemiology of the pediatric

EoE in other parts of the country [4–6]. Results from our parent-child cluster analysis underscored the influence of parental allergies on the development of EoE in their offspring. In particular, a history of childhood onset of paternal allergies appears to be a unique and an important risk factor associated with occurrence of EoE in their children.

In children under 18 years of age and living in United States, the prevalence of food allergies increased from 3.4% in 1997–1999 to 5.1% in 2009–2011 and the prevalence of skin allergies increased from 7.4% in 1997–1999 to 12.5% in 2009–2011. There was no significant trend in respiratory allergies from 1997–1999 to 2009–201, yet respiratory allergy remained the most common type of allergy among children throughout this period (17.0% in 2009–2011) Overall Hispanic children had a lower prevalence of food allergies (3.6%), skin allergy (10.1%), and respiratory allergy (13%) compared with non-Hispanic children white and non-Hispanic black children [7].

The children of Texas and adjoining southwestern states represent an important component of the pediatric population in the US. The southwestern U.S. total child population expanded by 61.4% from 1970 to 2010, compared to 6.5% increase in the total child population in the US. The children living in this area have a unique demographic, racial/ethnic-mix, and health characteristics (such as childhood obesity) and health care utilization profile (such as access to higher level of health care). Furthermore, over the past decade, in Texas, significant growth has been reported in Hispanic children [8]. In our study, while EoE affected children belonging to all ethnicities, a relatively high prevalence was observed in Caucasian children and it disproportionately affected males. In contrast, the Hispanic children had a lower prevalence of EoE as well as food and environmental allergies compared to other non-Hispanic white children or non-Hispanic black children. Furthermore, in our patient population children belonging to other ethnicities tended to be younger than the Caucasian children. Similar observations have been made in adult EoE patients [9]. This raises an important question about the possibility of race/ethnicity, age and possibly cultural differences being a confounding factor in development of EoE not only in adults but also in children.

Over 30% of our patients were allergic to multiple allergens. The majority of children with EoE had associated atopic comorbidities, and the prevalence of food allergies was higher than that of environmental allergies. These observations from our center concurs with the previously reported observations from other parts of the country [10,11]. Interestingly, over 50% of our patients had already undergone allergy testing (e.g., skin prick test) for food and aeroallergen sensitivity prior to being seen in our center, more than likely the result of many of our patients being referred by community allergists.

A history of asthma in the immediate family is one of the major risk factors for childhood asthma, and the same is true for atopic eczema and allergic rhinitis. A recently published large prospective study reported a sex-dependent association of parental allergic conditions with childhood allergies, with maternal allergy increasing the risk of allergies in girls and paternal allergy increasing the risk of allergies in boys [12]. Observations from our parent-child cluster analyses draw attention to a potentially similar phenomenon occurring in EoE. In particular, it raises a question about a gender-based differential effect of paternal atopy

among children predisposed to EoE. Plausibly, this differential effect could possibly be due to a combination of several factors such as sex-dependent genetic differences (single nucleotide polymorphism in a gene coding thymic stromal lymphopoietin on the pseudoautosomal region of the X and Y chromosomes) and/or epigenetic influences (timing and nature of food and aeroallergen exposure) [13].

Results from this study must be interpreted with caution. Our observations from the retrospective study are limited by the nature of the study design. However, we attempted to minimize the effects of the retrospective design by creating a definite research question, clearly defining our EoE cases, using a standardized data abstraction form and developing clear inclusion and exclusion criteria. The findings regarding the relationship between prevalence of parental allergies and occurrence of EoE in their offspring are not definitive due to small sample size, convenient sampling, recall bias, lack of control group, and lack of validated questionnaire to gather relevant data. However, they allow us to generate new etiologic hypotheses.

In conclusion, the characterization of our pediatric EoE patient population adds to the existing literature and contributes towards advancing our understanding of the clinical epidemiology of this complex clinicopathological condition. The results from the parent-child cluster analysis underscores the need for accurate assessment of the heritable risk in order to provide a more accurate diagnosis to parents, identifying at-risk children for preventive measures, and also investigating how environmental factors might interact with the patient's genetic predisposition. Future studies aimed at examining the potential differential influence of parental allergies on risk of EoE among children are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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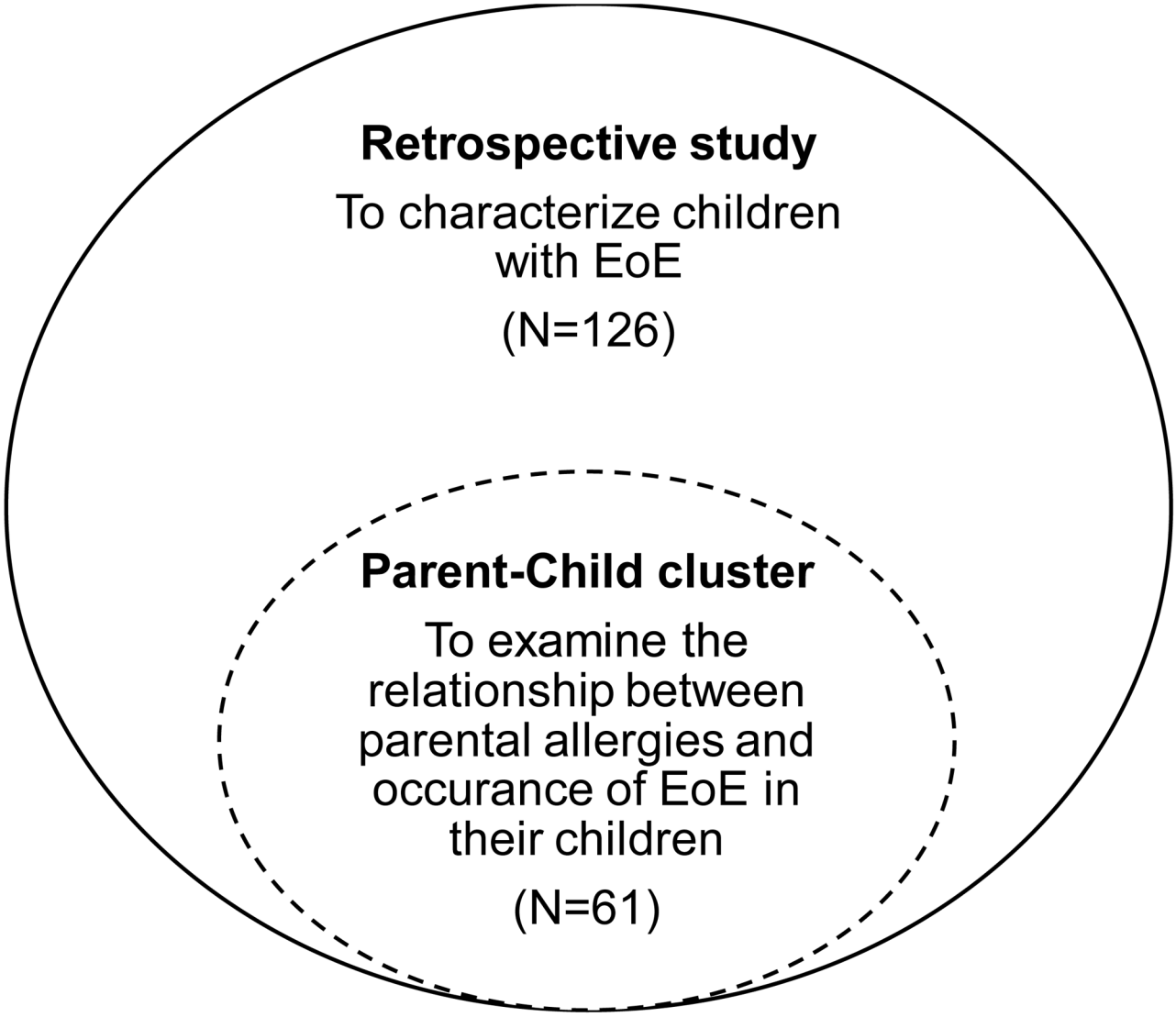

Figure 1.
Schematic representation of the study

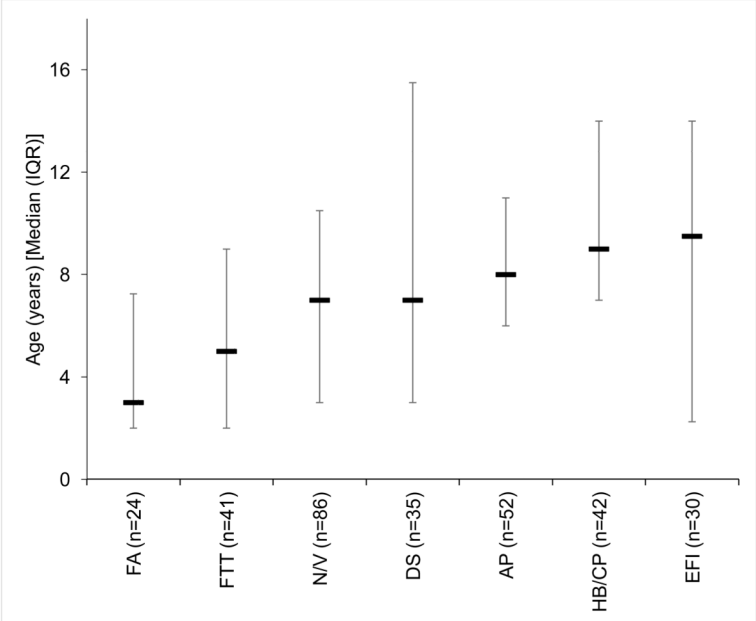

Figure 2.

Relationship between age and presenting symptoms in children with eosinophilic esophagitis (N=126)

FA: Food Allergies; FTT: Failure-to-thrive; N/V: Nausea/Vomiting; DS: Difficulty Swallowing; AP: Abdominal pain; HB/CP: Heartburn/Chest pain; EFI: Esophageal food impaction.

Table 1

Characteristics of children with eosinophilic esophagitis included in retrospective study (N=126)

Age (years)	
Mean ± SD	8.67 ± 5.12
Median (25^{th} –75^{th} percentile)	8 (4 – 13)
Gender [n (%)]	
Male	90 (71)
Female	36 (29)
Ethnicity [n (%)]	
Caucasian	74 (59)
African American	18 (14)
Hispanic	13 (10)
Asian	4 (3)
Other	9 (7)
Allergic Co-morbidities [n (%)]	
Food Allergies	74 (59)
Allergic rhinitis	57 (45)
Eczema	51 (40)
Asthma	48 (38)
Environmental Allergies	31 (25)
Allergen(s) identified by skin prick test* (n=66; 52%)	
1 allergy	28 (22)
2 allergies	6 (9)
3 allergies	3 (4)
4 allergies	40 (32)

*Skin prick test for aero- and food-allergens [e.g., pollen, dust, mold and standard food allergen panel].

Table 2

Allergy profile of biological parents of children with eosinophilic esophagitis (Parent-child cluster; N=61)

Prevalence of allergies [n (%)]	
Mother +/Father −	20 (33)
Mother −/Father +	11 (18)
Mother +/Father +	17 (28)
Mother −/Father −	13 (21)
Father +/Mother + or Mother −	28 (46)
Mother +/Father + or Father −	37 (61)

	Paternal (n=28)	**Maternal (n=37)**
Onset [n (%)]		
Child	20 (71)*	23 (62)
Adult	7 (3)	11 (30)
Allergic conditions [n (%)]		
Eczema	23 (82)	34 (92)
Asthma	22 (76)	33 (89)
Food allergies	5 (18)	9 (24)
Allergic rhinitis	7 (39)	15 (41)
Environmental allergies	21 (75)	30 (81)
Eosinophilic esophagitis	2 (7)	2 (5)
Eosinophilic gastroenteritis	--	1(3)
Eosinophilic colitis	1 (4)	--

* Paternal: Childhood vs. Adult onset of allergies (P value = 0.03). All other comparisons statistically non-significant (P value > 0.05)