Distinct Features in the Clinical Presentations of Eosinophilic Esophagitis in Children and Adults: Is This the Same Disease?

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Key Words

Dysphagia · Eosinophil · Food impaction · Esophagus

Abstract

Recent consensus guidelines define eosinophilic esophagitis (EoE) as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Adults with EoE typically present with dysphagia, food impaction and reflux symptoms, while children primarily present with refractory reflux, abdominal pain, vomiting and growth failure. Endoscopic features are also somewhat different in adults and children. Adult patients often present with fibrostenotic features of EoE including rings, strictures and narrow-caliber esophagus, while children present with inflammatory features of EoE including edema, white exudates and furrowing. Despite these differences in symptom and endoscopic presentation, many similarities exist between the two groups suggesting that this is the same disease in both children and adults. First, atopic history and genetic predisposition have been demonstrated in both groups. Most convincing is that both adults and children respond to food allergen avoidance, implicating a common etiology in the pathogenesis of this disease. While additional data is needed to better understand the natural history of EoE, preliminary data suggests that EoE is the same disease in adults and children, but with different phenotypic presentations.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disorder characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation isolated to the esophagus [1]. This condition can affect both adults and children and the question arises whether this is the same disease in these two cohorts. In order to address this question, comparisons between the two groups in the areas of epidemiology, clinical and endoscopic presentation, pathophysiology, and outcomes will be addressed. While for many years EoE was thought to be mainly a pediatric disease, there have been a rising number of cases of EoE seen in both the adult and pediatric populations [1]. While these numbers seem to be at epidemic rates at academic tertiary centers, this is not a phenomenon just isolated to referral centers, but rather a global disease with cases being reported from all continents, with the exception of Africa. Recent estimates from population studies in Ohio and Switzerland suggest prevalence rates of 10.4/10,000 and 4.5/10,000 in children and adults, respectively [2, 3]. Because there can often be a delay of diagnosis or underrecognition of this condition in adults, this number in adults is likely an underestimation of the true prevalence of the disease [4].

Clinical Features

Similar to children, this is a male-predominant disease in adults with a 3:1 ratio. While cases of EoE are being recognized in all ethnicities, there is a Caucasian predilection in both children and adults [1]. Up to 70–80% of children and adults with EoE may exhibit other atopic conditions as well as a family history of either EoE or atopy [2]. Adults typically present with symptoms in the third or fourth decade of life, with the predominant symptoms being dysphagia (70–80%) and food impaction (33–54%) [1, 5]. Other symptoms include heartburn, reflux and chest discomfort. This is in contrast to children who typically present with reflux symptoms, vomiting, abdominal pain or failure to thrive [6]. Dysphagia and food impaction are noted less commonly in children. Several studies have also nicely shown that symptoms in children vary by age with younger children typically presenting with symptoms of feeding disorder, reflux and failure to thrive [2, 6, 7]. As the age bracket increases to school-age children, vomiting and abdominal pain start to become apparent and it is not until early adolescent and teenage years that children present with dysphagia and food impaction. Some speculate that this is due to the fact that young children are not able to properly articulate their symptoms and therefore just complain of abdominal pain. However, this could nicely represent the natural history of EoE as it progresses through childhood, with younger children presenting with reflux symptoms and vomiting, and as the disease progresses into adolescence, symptoms of dysphagia and food impaction, typical of the adult phenotype, emerge.

Our center speculated that this could be the result of changes in the topography of the esophagus between adults and children. In order to answer the question of whether adults and children have different endoscopic presentations, we analyzed these features in a pediatric and adult EoE population at Northwestern University [8]. We analyzed 320 patients (200 adults/120 children) seen at our center. The average age of the adults and children were 39 years (range: 17–79) and 4.7 years (range: 0.3–17), respectively. Both groups were predominantly male (74–75%) as is reflective of the EoE population in general. The average duration of symptoms was 8.3 ± 6 years in adults and 1.2 ± 1.5 years in children. Interestingly, 73% of children with EoE presented with peripheral eosinophilia versus only 11% of adults. The most common endoscopic features in adults were concentric rings (82%) and linear furrows (70%). Very few adults had white plaques (14%), and only 1% had a normal ap-

pearing esophagus. This was in contrast to the children whose most common endoscopic features were furrows (39%), white plaques (35%) and a normal esophagus (30%). Only 3% of the children presented with mucosal rings. In order to assess if this was an age-dependent phenomenon, we then broke this data down by age. What we found was that while mucosal rings were present across all categories in adults, they were only seen in older children and teenagers. Furrows were equally present across all age categories and interestingly, while white plaques were seen across all age categories in children, they were only present in the young adults. This gives further support that the symptom variation by age is due to changes in endoscopic features between the two groups. These presentations therefore likely reflect the natural history of this condition with younger patients presenting with the more inflammatory features such as white plaques, which may ultimately progress to fibrostenotic features such as rings and strictures as time goes on and they become adults.

Natural History

What is currently known about the natural history of EoE is that it is a chronic relapsing condition in both children and adults [6, 9]. In adults, complications that arise are typically stricture formation (11–31%), food impaction (30–55%), narrow-caliber esophagus (10%) and esophageal perforation either spontaneously from retching during a food impaction or postprocedurally from an esophageal dilation [1]. Due to the fibrostenotic changes in the esophagus, this can have a significant impact on the quality of life in adults. Patients may have stress over their symptoms, fear of food impaction and stigma over this relatively new diagnosis. Some adult patients may modify their eating behavior or avoid social situations where eating is involved so as to avoid a food impaction [10]. This behavioral modification may lead to a delay in the time to seek medical attention in some adults, leading to a delay in diagnosis.

This is also a chronic condition in children, who are unlikely to grow out of this condition [6]. Complications can arise such as poor nutritional intake, failure to thrive and growth retardation. Due to lack of palatability of the elemental formula, percutaneous gastrostomy tube placement may be necessary in some cases and the cost of therapeutic interventions both with endoscopy and PEG placement can be substantial. Children also experience significant psychological distress over fear of eating.

Avoidance of food and social situations where food is involved can also lead to a reduction in quality of life for many children [11].

Pathophysiology

The question has arisen in the field of EoE as to what triggers ensue to cause eosinophils to infiltrate into the esophagus and cause the esophageal dysfunction that is seen in both children and adults. Studies suggest that acid exposure, environmental factors and genetics may all play a role [1]. A complex interplay of acid exposure and development of esophageal eosinophilia and EoE has been noted [12]. Prior studies have suggested that higher levels of eosinophils were more indicative of EoE, while lower levels of eosinophilia were more consistent with gastro-esophageal reflux disease. However, recent studies in both the adult and pediatric population suggest that this relationship may not be as clear-cut. Ngo et al. [13] have previously shown that even high levels of esophageal eosinophilia may be resolved in pediatric patients presenting with a characteristic phenotype of EoE. This responsiveness of esophageal eosinophilia to acid suppression was also seen in a recent study of 35 adults in Spain with high levels of esophageal eosinophils [14]. Interestingly, 75% of the patients had resolution of esophageal eosinophilia, 50% of whom had a characteristic EoE profile. A 30% response was also seen in patients with a normal pH study, suggesting that the response to acid suppression may not be solely due to control of acid reflux. These studies have laid the groundwork for the condition of 'proton pump inhibitor-responsive esophageal eosinophilia' and have substantiated the need for the use of acid suppression prior to diagnosing EoE [1].

Role of Environmental and Food Allergens

Prior studies have shown that the prevalence of atopy in both children and adults is 70–80% in most cohorts [1]. Pooled studies have shown ranges of asthma and allergic rhinitis in adults with EoE to be 12–38 and 17–70%, respectively, numbers which are significantly higher than that reported in the general population [1]. Pooled studies have also shown that children with EoE have a higher prevalence of asthma (38–66 vs. 8.5%), allergic rhinitis (30–93 vs. 25%) and atopic dermatitis (19–55 vs. 10%) compared to the general population [1]. Studies in both adults and children have shown that both cohorts may

have positive allergy testing to both environmental and food allergens, but caution needs to be applied in order to best interpret the significance of this reactivity as studies have shown a poor correlation with certain allergy testing in identifying food allergens in EoE [5, 15, 16].

Food allergens have long been linked to the development of EoE in children, and a landmark study by Kelly et al. [17] in 1995 showed resolution of EoE after treatment with an elemental or amino acid-based formulation. Since then, several studies have replicated this finding showing a clear association between foods and EoE [18, 19].

While food allergens as a trigger for EoE in adults was previously thought to be controversial, several studies have shown a clear association. In the first prospective dietary study by Gonsalves et al. [8], a six-food elimination diet was highly effective at controlling symptoms, endoscopic changes and histology in adults with EoE. After just 6 weeks on the diet, 70% of the patients had eosinophil counts <10/high-power field. Reintroduction of food triggers not only recreated symptoms, but also histology and endoscopic features, showing a clear association that foods were driving this disease in adults as well. This finding has been substantiated by Lucendo et al. [15] who studied an empiric diet in their Spanish cohort and saw similar results (74% <15 eosinophils/high-power field).

Food reintroduction studies after dietary elimination also showed that the most common food trigger agents are similar between adults and children. The most common food triggers in children were milk, wheat, soy and egg [20]. In adults, the most common triggers were wheat, milk, soy, nuts and egg [8]. With these studies, it is now clear that food allergens are implicated in the development of EoE in both adults and children.

Role of Genetics

A genetic link for EoE was initially speculated due to the high incidence of both children and adult patients with family members with EoE and family members with atopy [2, 21–23]. Since these initial case reports, sophisticated genetic studies have been undertaken involving a whole genome microarray expression implicating that both adults and children with EoE have a unique genetic profile compared to patients with reflux and controls [24]. For instance, increased levels of a key upregulated gene, eotaxin-3, have been seen in both pediatric and adult cohorts [25, 26].

Conclusion

EoE can affect both adults and children, and the question arises as to whether this is the same disease in these two cohorts. The incidence and prevalence of EoE have been rising in both the adult and pediatric populations with reports suggesting that this is a global disease in both groups. Adults and children with EoE have a distinct clinical and endoscopic presentation which may explain some of the differences in symptom presentation. Immune dysregulation, environmental factors, food allergens and genetics have been implicated in the pathogenesis of this disease in both children and adults. Studies to

date have suggested that this is a chronic disease in both cohorts with a significant impact on quality of life. Additional longitudinal and natural history studies are needed to firmly address the question of whether EoE is the same disease in children and adults. The current data suggests that it is the same disease; however, children and adults likely represent a different phenotype or spectrum of this disease.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.

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