

Confounding factors affect the pathophysiology of eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis is a newly diagnosed esophageal disease in adult and children. The clinical and pathological characteristics of this disease have been established and were recently summarized in the expert clinical guideline published in 2011. In spite of the wide knowledge accumulated on this disease, there are many areas where scientific data are missing, especially in regard to the disease's pathophysiology. Recent publications have suggested that other confounding factors modify the disease and may affect its clinical-phenotypic presentation. Those factors may include place of living, air pollution, race, genetic factors and other. In the present report we discussed and review those confounding factors, the new developments, and what direction we should go to further advance our knowledge of this disease.

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INVITED COMMENTARY ON HOT ARTICLES

Eosinophilic esophagitis (EoE) is a chronic esophageal disease associated with allergy in adults and children. The clinical, endoscopic, and histological characteristics of EoE has been described and documented in several expert reports^[1,2]. In spite of the knowledge accumulated on this newly discovered disease, double blind placebo control studies have demonstrated that only about 50% of the patients will respond to therapy (biologic, steroids)^[3,4], demonstrating the existing gap between the clinical and/or basic knowledge, proposed therapy and the pathophysiology of EoE. The complete story of EoE in children is yet to be unfolded.

In a recent publication, Sperry *et al*^[5] compared the clinical presentation of EoE in a cohort of adult and pediatric patients diagnosed with EoE. The authors suggested that African American (AA) patients were younger at diagnosis, presented with failure to thrive (FTT), and were less likely to have esophageal rings compared to the Caucasian (C) patients^[5]. The paper has raised the possibility of other unknown confounding factors that may influence the clinical/phenotypic presentation of EoE in adults and children. Indeed, reviewing the

literature of EoE disease suggested that various factors may modify the disease incidence, clinical presentation, and/or clinical response to therapy. Those possible confounding factors are the topic of this paper (Table 1).

Epidemiological studies have showed that the disease's rate is unevenly distributed among adults and children living across the United States. The data showed that the prevalence of the disease in the North-Eastern states is higher in comparison with the South-Eastern states^[6-8]. Moreover, further analysis demonstrated that EoE is more prevalent in urban/sub urban areas compared to rural areas^[6,8,9]. The data suggested that there are environmental factors that modify EoE, but to date, those modifiers have not been clearly analyzed. The current geographic distribution may implicate air pollution as a modifier factor for EoE^[10]. Indeed, animal and clinical studies have confirmed the essential role of aero-allergens in the pathophysiology of the disease^[11-13]. Few investigators reported an increase incidence of EoE during the allergy seasons (low during winter, high during spring and fall)^[14-16], but those findings were not confirmed by others. For example, in a recent preliminary report, Frederickson *et al*^[17] reviewed esophageal biopsies in a cohort of 19 172 patients in Iowa City, IA, of whom 167 adults had EoE. The author reported a comparable monthly rate of EoE with no seasonal variation. Using a national pathology laboratory data base, the seasonal trend of 9995 adult patients was examined by others who reported a similar monthly and seasonal distribution of the patients diagnosed with EoE^[18]. Similar results were described by investigators who performed an internet search to look for EoE and seasonal variation^[19]. In a recent study, Hurrell *et al*^[20] reported a higher prevalence of esophageal eosinophilia in adults who live within the colder geographic zones of the United States compared to those living in the warmer climates. They implicated that the specific flora grow in those areas generate highly potent aeroallergens, and is responsible for their findings. In contrast, the United States governmental environmental agency (Environmental Protection Agency, National Oceanic and Atmospheric Administration, National Park Service) reported the lowest air pollution in the northern geographic areas of the United States, those with colder climate rather than the warmer climate (<http://airnow.gov>).

In addition to the possible role of aeroallergens and pollution in the pathophysiology of EoE, clinical reports have documented the etiologic role of food allergy in this disease^[3,11,21-23]. Indeed, the updated clinical guideline recommended checking food allergy in any patient who is newly diagnosed with EoE^[1]. Moreover, in support of this role, eliminating the food allergens alone (i.e., hypoallergenic formula) resolved the clinical symptoms and reversed the histological changes typically seen in EoE^[1,24-26]. In patients that would not accept this mode of therapy, topical or systemic steroids are suggested^[1]. In a randomized, double-blind, placebo control study, EoE children were treated with Fluticasone propionate^[3].

Table 1 Confounding factors and eosinophilic esophagitis

Factor	Ref.
Geographic distribution	[6-9,20]
Air pollution (aeroallergens)	[11-13]
Food allergy	[21-23]
Race (ethnicity)	[27-35]
Gender	[21,26]
Genetic factors	[22,23,39,40]

The authors showed that the children with no allergy had a better response to therapy compared to the children with allergy, pointing towards the role of food allergens as modifiers^[3]. Indeed, the role of food allergens in the pathophysiology of EoE has been established, but we are still lacking the exact function of these modifiers. Are all food allergens equal? What about the EoE patients who tested negative for any allergy? Is their disease is more benign? Do they achieve symptom control easier? All these questions are still unanswered and need further investigation.

The different distribution of EoE among various ethnicities has been previously published in adults and children. For example, the clinical presentation of EoE in children reported from several United States centers showed a statistically higher disease rate in C compared to AA or hispanic^[21,27-29]. Other reported similar findings in the adult population^[5,30,31]. This discrepancy is further accentuated by the epidemiologic data showing that in spite of the wide global distribution of EoE, very few reports from the African continent or from the east Asian countries were reported^[1,32-34]. In recent years we have assessed the different clinical presentation of EoE between AA and C children. In that study, we compared between AA children living in urban neighborhoods in New York City and C children who are living in rural West Virginia^[35]. We reported that EoE in AA children presented at an earlier age, have more history of atopic features, and presented with significantly lower endoscopic features of EoE compared to the C children. Similarly, Sharma *et al*^[36] reported that AA children are more likely to present with FTT, gastroesophageal reflux disease symptoms, and at a younger age compared to the C children at the same cohort. Sperry *et al*^[5] compared the clinical presentation of EoE in a cohort of adult and pediatric patients diagnosed with EoE. The authors suggested that when compared with C children, AA children diagnosed at a younger age, present with FTT, and have less esophageal rings^[5].

Overall, these data suggest that racial factor does play a role in EoE disease and may serve as a modifier in the disease phenotypic presentation. Further studies will be needed to fully establish the role of ethnicity in the pathophysiology of EoE.

Male sex is the predominant gender in EoE^[1]. In large series, the male/female ratio was reported up to 3:1^[21,37]. The effect of gender on EoE disease has not been well investigated and studies on this subject are

lacking. Rothenberg *et al*^[38] suggested that the predominance of males in EoE may be related to the thymic stromal lymphopoietin receptor resided within the pseudoautosomal region 1 on the X and Y chromosomes (Xp22.3, Yp11.3). The author suggested that this region may explain the higher incident of male gender in EoE.

Similar to many other chronic diseases; i.e., inflammatory bowel disease, celiac disease, asthma, *etc.*, genetic factors have a significant influence on the prognosis of EoE. Indeed, several investigators evaluated the genetic factors related to EoE. Few investigators reported that EoE tends to cluster in families^[22,23], and other showed by genome-wide microarray expression analysis that EoE patients have a different spectrum of genes compared to children with gastroesophageal reflux disease or normal control^[39]. Others showed that specific genes are closely associated with eosinophil's activation and are increased in patients with EoE^[1,4,39,40]. In another study, Lu *et al*^[41] identified 32 different miRNA which are specific for EoE, of which miRNA-21 and miRNA-223 were the most up-regulated, and decreased post steroid therapy. In a preliminary report, Gonsalves *et al*^[42] reported that the esophageal epithelial barrier genes (Desmoglein 1) is lower in adults with EoE who did not respond to dietary therapy, suggesting a dysfunctional, leaking esophageal mucosa. The new data may explain the role of aeroallergens in the disease's pathophysiology, by permitting the absorption of allergens (aeroallergens or food allergens) through the tightly sealed epithelial layer of the esophagus, and/or may explain the quick absorption of topical steroid into the esophageal mucosa during therapy.

Overall, the genetic framework involved in the pathophysiology of EoE is emerging and the genes responsible for activation or suppression of the inflammatory process are slowly uncovered. Nevertheless, we still have a large gap of knowledge left to explain the different response to therapy in EoE patients who belong to a different gender, different ethnicity, or have different allergies.

In summary, eosinophilic esophagitis is a chronic disease of the esophagus with clinical and histological characteristics previously established and described^[1]. As in many chronic diseases, the clinical and/or histological presentation may be altered by various environmental or genetic modifiers. Epidemiological and clinical reports have documented the different phenotypic presentation of EoE in different populations, but further investigation is needed to dissect those disease modifiers in order to be able to tailor therapy for the specific patient. In the era of personalized medicine these modifiers play a crucial role in the disease's prognosis, and future studies to address those factors are clearly warranted.

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