EOSINOPHILIC OESOPHAGITIS: FROM RARE TO COMMONPLACE, WHAT ARE THE POTENTIAL EXPLANATIONS?

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ABSTRACT

In this century, eosinophilic oesophagitis (EoE) has become a more recognised allergic disease, resulting in the publication of two consensus reports as the information of its pathophysiology has been rapidly elucidated. Its initial appearance in medical literature was in the 1970s, but it was not until the late 1990s that its paediatric-to-adult spectrum became more evident. Currently, it is a commonplace diagnosis in gastroenterology clinics, and the management of the disease commonly involves allergists. Coming from humble beginnings, the true reasons for its emergence on the worldwide allergic diseases stage is not understood. This review explores possible explanations of the origins of EoE. As food intolerance is an important component of EoE, the role of modern food production is discussed, as well as elements of EoE that have been possibly overlooked.

Keywords: Eosinophilic oesophagitis (EoE), children, adolescent, adult, food allergy, microbiome, immunoglobulin E (IgE).

INTRODUCTION

A rare occurrence in allergic and gastrointestinal disease clinics at the beginning of the 21st century, eosinophilic oesophagitis (EoE) is now a commonplace diagnosis for allergists and gastrointestinal specialists. Publications strongly support a marked increase in both incidence and prevalence, and unfortunately, there is scant evidence that once diagnosed it will ever go into permanent (or spontaneous) remission. In many ways, EoE is the worst of all possible chronic allergic conditions.[1] It behooves investigators, therefore, to consider what potential changes in modern society could possibly have occurred to allow for an essentially new allergic disease to emerge. We comment on the current understanding of EoE epidemiology, genetics, clinical presentation, and treatment, with an emphasis on the factors that may have allowed a new target organ (oesophagus) to be subject to the allergic processes that have involved lungs, nose, and skin for hundreds of years.

DEFINITION OF EOSINOPHILIC OESOPHAGITIS

The 2011 consensus guidelines stated that EoE "represents a chronic, immune/antigen-mediated disease characterised clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation."[2] Currently, no studies have been forthcoming that explain what causes an antigen, largely foods, to cause a near-permanent change in oesophageal function with associated eosinophilia. Based on studies, once EoE is initiated, the genomic pathway cannot be turned off without a discovery of which food or foods must be totally avoided. The ability for foods to overcome established tolerance, and induce a fixed change in genomically regulated eosinophilia chemotaxis and loss of barrier function in the oesophagus is a remarkable accomplishment.

EOSINOPHILIC OESOPHAGITIS: A TRULY BRIEF HISTORY

Two articles published in consecutive years appear, in hindsight, to be the initial two patients with reported EoE.[3,4] Other eosinophilic gastroenteritis diseases had been recognised before that time, but these two cases appear to be the first EoE reports.

Subsequently, sporadic cases appeared in the literature in the 1980s along with the observation that gastrointestinal reflux disease was related to eosinophilia in adults and children. Eventually a collection of 11 EoE cases was published in 1985, which included adults and children with oesophageal eosinophilia and reflux.[5] The author concluded that: "Idiopathic EoE is an unusual variant of idiopathic, but presumably allergic, eosinophilic infiltration of the gastrointestinal tract."

In the early 1990s, a unique group of adults with significant dysphagia and oesophageal eosinophilia were reported.[6] The authors concluded this was a "distinctive clinopathological syndrome not previously described." The number of eosinophils that can be seen in normal and asymptomatic atopic children in the oesophagus was established as zero in 2006, with a gradient eosinophilia in all other gastrointestinal sites beyond the oesophagus.[7] The presence of gastrointestinal eosinophilia beyond the oesophagus suggests a biological function and an evolutionary advantage for their presence; and, conversely, a non-necessity of having any eosinophils adaptively in the oesophagus. The first consensus guidelines for EoE were published in 2007.[8] A 2014 insurance claims analysis of EoE estimated a prevalence of 56.7/100,000 persons in the USA.[9]

In summary, the literature suggests that a new, or previously totally unrecognised, oesophageal-targeted allergic disease first appears in the later decades of the previous century, hundreds of years after other well-recognised and characterised allergic diseases.

GENDER OF THE EOSINOPHILIC OESOPHAGITIS POPULATION

The most obvious finding in EoE subjects is the strong male dominance in all age categories. Unlike asthma, which has male dominance until puberty, with an abrupt shift at puberty and through adulthood to a female dominance, EoE maintains its male dominance in all age groups. Other common allergic diseases such as food allergy, allergic rhinitis, and atopic dermatitis do not demonstrate male dominance. A genetic study of EoE refuted Mendelian inheritance, although in nuclear families father-to-son and brother-to-brother was more common than female-to-female association.[10] Because atopy was also a common finding, a complex genetic explanation was concluded.

Thymic stromal lymphopoietin (*TSLP*) has been implicated as an important genetic variant to be associated with EoE risk.[11] The *TSLP* gene is on chromosome 5q22, while the gene for the receptor for TSLP is encoded on a pseudoautosomal region on Xp22.3 and Yp11.3.[11] These findings may sufficiently explain the consistent male dominance for developing EoE.

THE INDUSTRIAL NATIONS' DOMINANCE OF EOSINOPHILIC OESOPHAGITIS POPULATIONS

EoE is almost exclusively reported in developed nations with a frequent comorbidity of other allergic diseases. The story of increased allergic disease in developed countries has concomitantly resulted in explanations based on the 'hygiene hypothesis' of allergic disease.[12] The ability for food avoidance protocols to modify oesophageal eosinophilia in EoE in different countries points to near unanimous concern that the environmental cofactors allowing EoE are shared in populations across industrial nations.

Although the association between first world status and EoE is well recognised, local associations within a specific country are limited. A study of predominately adults with EoE in continental USA demonstrated a strong association of EoE to rural areas.[13] These findings need replication, including in children, to further support a rural/urban dichotomy. Interestingly, there is a costal similarity in airborne microbiota (bacteria and some fungi) as compared with central USA, which parallels the urban versus rural presence of EoE.[14] These findings might suggest geographical differences in intra-oesophageal microbiome; however, control subjects for an EoE microbiome study from Colorado and Illinois had no difference in microbiome.[15]

OESOPHAGEAL MICROBIOME AND EOSINOPHILIC OESOPHAGITIS

There exists a generous microbial load in the normal oesophagus.[16] Studies have demonstrated a similar microbial flora as in the mouth.[16] A subsequent report demonstrated a dysbiotic microbiome in oesophageal diseases.[15] The oesophageal microbiome in adults and children with EoE is also altered, as is the microbiome of adults with asthma as compared with non-asthmatics.[17,18] It is also possible that the oesophageal microbiome could be altered due to presence of an eosinophilic-induced cationic state in active EoE.

The pathological flora of a *Clostridium difficile* infection can be altered using faecal transplants. Equally, the ability to repopulate the oesophagus with normal resident flora in situations of disease-related dysbiosis could be considered, especially after treatment has returned the oesophagus to a non-eosinophilic state. Restoring a normal microbiome could affect the natural history of EoE. It is also possible that neither swallowed corticosteroid treatment nor successful remittive food avoidance therapy may return the dysbiotic microbiome to normal.

WHAT HAPPENS AFTER THE 'BIG BANG' IN EOSINOPHILIC OESOPHAGITIS?

It is unclear what event or series of events allows the eosinophilic potential of the oesophagus to be unlocked. In contrast, the downstream events after the 'big bang' have been well-studied.[19] There is a pathological synergy in oesophageal barrier dysfunction coupled with an intense T helper cell Type 2 (Th2) inflammation. The Th2 immune response is remarkably similar in all ages, sexes, family associations, and likely races. Barrier function genes are downregulated, especially for filaggrin, zonulin, and adhesion molecules.[11] Loss of function mutations in filaggrin are common in Europeans and Asians but these variants are not seen in Western African-Americans.[20] The ethnic genetic variants for filaggrin loss of function mutations not found in African-American children could possibly suggest mechanisms that protect against EoE development. Coupled with primary or secondary barrier dysfunction is an intense Th2 cellular and cytokine infiltration. Mast cells, basophils, and of course eosinophils are increased, along with their inflammatory responses. Chief among the multitude of genomic changes seen in EoE are upregulated genes with functional activity in mucosal tissue: *eotaxin-3*, *TSLP*, and *calpain*.[19] Mast cell and Th2 lymphocyte cytokines interleukin (IL)-4, IL-5, and IL-13 are active in promoting immunoglobulin (Ig)E production and eosinophilia.[19]

Transcriptome studies have strongly supported an upregulation and downregulation pattern of specific genes in the mucosa of subjects with EoE. This dysregulated pattern is largely modifiable by therapy, but presumably reverts when therapy is discontinued. Obviously, the genomic switch that occurs at the onset of disease maintains a marked dysfunction, as EoE rarely spontaneously remits. It again confirms that the 'big bang' that induces EoE has a lasting effect.

ANTIBODY ASSOCIATIONS IN EOSINOPHILIC OESOPHAGITIS

IgE associations are common to the pathogenesis of EoE.[11,19,21] However, a recent review of IgE in different allergic diseases stresses that levels of IgE to food are lower in EoE compared with other food associated allergic diseases.[22] As previously discussed, intense Th2 immunity is a hallmark, and IgE activity against foods is commonly identified by allergy skin testing.[21] Patch testing for foods provides additional information, but the mechanism resulting in a positive response is unclear.[21] In certain situations, milk is both IgE negative and patch negative, but must be included in the avoidance list for maximum clinical response.[21] Recently, adults and children with EoE have demonstrated an antibody IgG4 to food, and granular mucosal deposits for the same Ig.[22-24] Also, the potential for explaining positive food patch testing using IgG4 localisation would be intriguing. Caution for the IgG4 phenomenon in EoE has been raised.[25]

AEROALLERGENS AND EOSINOPHILIC OESOPHAGITIS

Early in the discussion of EoE induction there was speculation that ingested aeroallergens might be an important factor. A case report was published and concern for an equivalent to oral allergy syndrome was suggested, while a further investigation suggested a link between pollen exposure and EoE seasonal diagnosis.[26,27] Extensive evidence of wide applicability for this concept has not advanced, and most investigations have pointed to food antigen stimulation, both with IgE, non-IgE, and T cell activation associations.

LOCAL IMMUNOGLOBULIN E PRODUCTION

Local IgE production has been shown to occur in some individuals with chronic rhinitis without a systemic IgE presence, and in nasal polyposis.[28,29] In fact, similar findings have been shown to occur in EoE.[30] If true, local oesophageal IgE presence could result in frequent interaction with swallowed antigen, i.e. foods, resulting in a Th2 target organ response. This potentially could explain why using an elemental diet, which halts all food exposure, allows for downregulation of the local allergenic response. In the future, component-resolved diagnostics may provide patient-specific food avoidance protocols. This technology has shown allergen responsivity in vernal conjunctivitis.[31] However, the use of allergen-microarray-guided dietary therapy proved unsuccessful in an adult study.[32]

The explanation for positive patch tests to foods has however not yet been explained using the conventional concepts of early and late phase IgE responses. It is possible that avoiding patch positive foods may identify those foods that only have a local IgE response or by identifying T cells sensitised to the food. Alternatively, it remains to be determined if IgG4 plays a role and/or causes positive patch food tests. A pertinent review of non-IgE mediated processes possibly involved with EoE has been recently published.[33]

THE EOSINOPHILIC OESOPHAGITIS SPECTRUM IS EXPANDING

The requirement to use a proton pump inhibitor to adequately support the clinicopathological diagnosis of EoE was proven with a recent study of the pathophysiology of proton pump inhibitor-responsive oesophageal eosinophilia (PPI-ROE).[34] There is, however, a report suggesting there is more similarity between EoE and PPI-ROE than was suggested by the report of Wen et al.[34,35] In contrast to the marked eosinophilia of the two known oesophageal entities, a new twist has emerged.[36] In a European centre, several EoE families had members with dysphagia and corticosteroid responsiveness, without eosinophilic infiltration, but with marked T cell and modest mast cell infiltration.[36] Expression of messenger RNA (mRNA) for *MUC4* and *CDH26* genes were different between the cases and control, and *eotaxin-3* mRNA was significantly different from cases and conventional EoE.[36]

Another recently described oesophageal condition, lymphocytic oesophagitis, has overlapping symptoms of EoE, but with a non-granulocytic, lymphocytic infiltration.[37] It appears to be PPI-responsive. Straumann et al.[36] suggested a common pathogenic similarity between EoE, lymphocytic oesophagitis, and EoE-like disease. It would also suggest PPI-ROE should be included.

OESOPHAGEAL MUSCULARIS PROPRIA REACTIVITY IN EOSINOPHILIC OESOPHAGUS?

Murine allergen-induced asthma models clearly demonstrate mucosal inflammation and smooth muscle hyper-responsiveness that mimics human asthma.[38] Human asthma demonstrates mucosal eosinophilia and bronchial reactivity. The chronicity of asthma, especially in atopic individuals, results in smooth muscle hypertrophy and hyperplasia, which enhances intrinsic bronchial reactivity. Foregut differentiation in human embryos forms the oesophagus and respiratory tract. It seems possible that beyond the similarities in mucosal and submucosal inflammation in Th2-induced asthma and EoE, oesophageal smooth muscle could have downstream hyper-reactivity in EoE as in asthma. The prolonged oesophageal motor dysfunction known to occur in EoE may share commonality with bronchial reactivity. In fact, intrinsic oesophageal motility disorders demonstrate hypertrophy of the muscularis propria.[39]

FOOD PRODUCTION AND EOSINOPHILIC OESOPHAGITIS

As numerous studies have shown food to be a prime driver of the eosinophilic state of EoE, it is critical to consider how food could induce immunological changes. Because the disease is greatly more complex than IgE-mediated food allergy, it appears that the complex pathophysiology of atopic dermatitis and asthma are better surrogates.

Breastfeeding likely provides temporary protection against infantile EoE. Although EoE occurs in infants, there has been no obvious shift in the incidence of EoE toward infants over the past two decades, suggesting that early milk exposure (e.g. formula) is not inducing a quick immunological

change. In the report of Kagawalla et al.,[40] a milk-only avoidance diet improved a subset of EoE children, suggesting that milk immunological activity was not an immediate life-altering event, and a period of time was required to result in clinically evident disease.[40]

If it is possible that a gradual complex multi-dimensional immunological reactivity to food induces EoE, looking at the food chain over the past three decades bears consideration. Studies of children with EoE show high prevalence of positive allergic reactions to milk, eggs, peanuts, and wheat.[21] Successful elimination diets avoid milk, eggs, peanuts, wheat, tree nuts, fish, shellfish, and soy.[2,21] A diet modification used in adults is avoidance of milk, gluten (wheat), legumes, and eggs.[41] The potential necessity of expanding wheat avoidance to all gluten products has been raised.[42] Also, expanding soy avoidance to legume avoidance has been investigated.[43] In most circumstances, a team approach to dietary management, including physician and dietician, is preferable for best outcome.

Concomitant with the increase in prevalence of EoE in developing countries over the past 30 years is the change in animal feeding practices. In particular, the dairy cow and commercial egg industries have moved to a large scale production model in the USA, with strict control of feeding schedule and materials. Current dairy cow diet can often include alfalfa (haylage), with varying curing techniques (fermentation), pelleted soybean pods, cottonseed, dried distillers grain (corn), wet gluten (corn), dried alfalfa hay, and straw.

Industrial poultry egg production relies on efficient feed management practices. Current poultry feed includes cereal grain meal (corn, wheat, etc.), vegetable protein sources (oilseed crops: soy, etc.), animal protein sources (poultry, cow, fish), lipids (soy oil, etc.), vitamins, and minerals.

The nutrient value of any food revolves around the protein, fat, and carbohydrate composition ingested, all of which might be subtly modified by animal feed composition. There is, however, no overwhelming evidence for modifications of any nutrient component, despite changes in animal dietary practices.

The final speculation of food modification involves processing. To enhance shelf-life, reduce microbial contamination, fat rancidity, and enhance palatability, basic staple foods, such as wheat and grains, have numerous preservatives and flavourings added. Gluten is often added to bread production. In essence, a wide repertoire of add-in products is eliminated when wheat (gluten grains) is eliminated, and that certainly is the case in an elemental diet protocol.

There is emerging human data that supports a food component causing a potential immunological response. A study of invariant natural killer T cells, which can produce Th2 cytokines from milk-allergic children showed these cells proliferate and induce Th2 cytokine secretion when incubated with cow's milk sphingomyelin and alpha-galactosylceramide.[44] Further work has shown the invariant natural killer T cell from untreated EoE children released Th2 cytokines when exposed to cow's milk-sphingomyelin and alpha-galactosylceramide.[45] These cells are present in oesophageal biopsies in EoE. A dairy science study showed that varying the diary cow's dietary intake can alter the phospholipid, sphingolipid, and fatty acid compositions of the milk fat globule membrane.[46] The cow diet rich in polyunsaturated fatty acids (linseed oil) had a 30% greater weight/volume concentration of sphingomyelin in their milk.[46] Currently however, there is no scientific evidence that any production process for any food can be implicated in the development of EoE.

Recent oral tolerance studies have unintentionally provided insight for the support of food as a trigger for EoE induction. EoE may occur in children undergoing reintroduction of a single food in oral tolerance protocols.[47] This reinforces the potential for a single food, with protein, fat, and carbohydrate reimmersion, to cause EoE. The component of the food that is inducing disease could be speculated to be protein (as they are all atopic), but lipid or even carbohydrate T cell responsiveness needs further investigation.

PASSIVE BYSTANDER THEORY

Having considered the development of EoE as a direct change in genomic (and epigenetic) expression of eosinophilic and Th2 cytokines,[48] another possibility exists. An epidemiological event, paralleling the appearance of EoE in medical literature, is the increase in other allergic diseases. Most paediatric and many adult patients with EoE have another allergic disease and/or are atopic. It is conceivable that EoE was always an extremely rare disease with no reasonable accessibility for diagnosis prior to the 1970s. As the burden of

other allergic disease continued, and the number of Th2-dominant individuals increased, this resulted in oesophageal genetic and epigenetic elements to be hyper-exposed to Th2 cytokines in increasing numbers of individuals. Eventually, the oesophagi in enough individuals were targeted sufficiently to allow for a recognisable (increased) prevalence. There are animal models that support the effect of Th2 cytokines on eotaxin induction in lung tissue.[49] In addition, IL-13 downregulates filaggrin expression in skin keratinocytes in mice,[50] also supporting the potential effect on circulating Th2 cytokines to eventually 'cause' EoE.

EXTRA-OESOPHAGEAL SYMPTOMS IN PAEDIATRIC EOSINOPHILIC OESOPHAGITIS

The upper gastrointestinal tract to the middle third of the duodenum is formed from the embryonic foregut. It seems empirically unlikely that a robust inflammatory disruption of the oesophagus in EOE would affect downstream gastrointestinal function. However, two studies have suggested that EoE can co-demonstrate extra-oesophageal symptoms. A recent manuscript details a standardised questionnaire (Pediatric Eosinophilic Esophagitis Symptom Scores [PEESS] v.2.0) for both EoE symptoms.[51] The EoE questionnaire used did not have questions on diarrhoea or constipation.[51] However, of the 46 paediatric subjects, 37% reported diarrhoea and 17% reported constipation. In a prospective study, Fernandez et al.[52] enrolled children with new EoE and atopic matched controls. Comparing paediatric EoE (n=25) and age and gender-matched allergic disease controls, 40% of the EoE children had constipation, 24% had diarrhoea, and 48% had abdominal pain.[52] The results of both studies suggest a downstream effect of EoE on gastrointestinal function, and a yet under-reported clinical comorbidity.

CONCLUSION

Currently an uncommon, but well-characterised allergic disease, EoE matches asthma and atopic dermatitis in its complexity. Much of the immunology and basic science investigation in these more common conditions has allowed for a rapid expansion of the scientific knowledge base of EoE. New information suggests other immunologically based oesophageal variants, and EoE may actually have phenotypes that rival the asthma cluster analysis studies. Its potential for life-long disease, unless treated, will result in multi-generational physician care, with paediatric and adult gastroenterology and possibly paediatric to adult-based allergy co-management. Still encouraging is the ability for a food elimination treatment plan to induce remission; but the truth behind the food induction of EoE needs co-operation from basic medical scientists and the food science industry. With the advancement in food industry practices in less developed countries, current EoE prevalence may be the beginning of an allergic disease epidemic.

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