

OPINION

Risk factors for eosinophilic esophagitis

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Summary

Eosinophilic esophagitis (EoE) is a chronic antigen driven disease, whereby food and/or aeroallergens result in inflammation and luminal narrowing, and the clinical symptoms of dysphagia and food bolus obstruction events (FBOE). Established risk factors are male gender, Caucasian race and atopy. Increased risk amongst family members, and a single nucleotide polymorphism (SNP) in a gene coding thymic stromal lymphopoietin (TSLP) on the pseudoautosomal region of the X and Y chromosomes supports a genetic predisposition. Environmental factors including the timing and nature of food and aeroallergen exposure to the developing immune system may be important, whilst esophageal barrier function integrity and the influence of microbiota are worthy of future research.

Keywords allergy, eosinophil, esophagus, antigen, remodelling

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Introduction

Eosinophilic esophagitis (EoE) is conceptualised as a chronic antigen-driven disease, whereby food and/or aeroallergens stimulate an eosinophil-rich infiltrate in the oesophagus that produces the clinical syndrome of dysphagia, feeding difficulties (in young children) and food bolus obstruction [1, 2]. EoE was first recognised as a distinct clinical entity only recently, in 1993 [2]. The epidemiology, basic scientific and clinicopathological data are hence somewhat limited, and to date, the most clearly defined risk factors for EoE are gender (male predominance), race (mainly a disease of white Caucasians) and atopy (elevated serum IgE to common aeroallergens and other allergic conditions (asthma, seasonal rhinitis and atopic dermatitis)). Other putative risk factors include alterations in barrier function (e.g. from gastroesophageal reflux disease (GERD), variation in the nature and timing of oral antigen exposure (e.g. secondary to infant feeding practices, proton pump inhibitor use and commercial food processing) and variation in the nature and timing of aeroallergen exposure (seasonal, geographical and secondary to migration and factors relating to fibrous remodelling (e.g. ACE gene polymorphisms and TGF- β polymorphisms)).

The reasons for this gender and racial difference are not known, but could include genetic factors transferred

on the sex chromosomes, mitochondrial DNA or possibly the pathoplastic effects of sex hormones on inflammation and fibrosis [3–6]. A history of EoE in a first-degree relative has been reported in 23–37% of cases (adult vs. paediatric), supporting a genetic basis, although a more modest familial trend was demonstrated recently (about 3%) [7, 8]. Genetic studies have been useful in correlating single nucleotide polymorphisms (SNPs) with a propensity to develop atopic conditions, including EoE. Notably, thymic stromal lymphopoietin (TSLP), eotaxin 3 and filaggrin SNPs appear to predispose to EoE, and a SNP for TGF- β predicts response to corticosteroids [9–11].

This review examines the basic scientific, epidemiological and clinical studies relating to the pathogenesis of EoE and attempts to highlight unexplored risk factors with a view to future research and therapeutic innovation.

Epidemiology – A Western disease on the increase?

The history of EoE is short. Prior to 1990s, only a few case reports of oesophageal eosinophilia had been reported, with Attwood, Levine and Saul, and Vitellas being amongst the first to suggest the existence of a distinct clinicopathological entity [2, 12, 13]. What is not known is if EoE is a disease of modern life, or if the

apparent increase in the last 20 years is a result of awareness by clinicians and researchers armed with modern endoscopic equipment able to make the diagnosis with the mandatory oesophageal biopsy. For example, some patients who were once assumed to have gastroesophageal reflux disease (GERD) with stricture formation may now be called EoE. To date, several large uncontrolled retrospective studies from North America, western Europe and Australia demonstrate an increasing incidence and/or prevalence of EoE [14–16]. Interestingly, other atopic conditions that are better characterised such as atopic dermatitis and food allergy *per se* have increased amongst children in the USA in the last 14 years [17].

Theories relating to the apparent increase in EoE are broad. They are mostly borrowed from research on other atopic conditions and relate to recent changes in living conditions and medical treatments, such as exposure to bacterial pathogens, moulds and animal antigens (i.e. the hygiene hypothesis), or a decrease of *Helicobacter pylori* infection in Western populations [18, 19]. Furthermore, use of proton pump inhibitors, a decrease in consumption of fresh fruit and vegetables and an increase in processed foods have also been suggested as causes for the apparent rise in allergic conditions including EoE [20, 21]. Whilst hypothesis abound, good quality prospective data collection in relation to EoE is needed before conclusions can be reasonably made.

Age, gender and genetics

EoE is a disease of both children and adults. The majority of cases diagnosed in childhood are between 5 and 10 years of age, although cases in very young children are seen [22, 23]. In adults, the mean age of diagnosis is in the late 30's, with almost all cases diagnosed before the age of 50 [15, 24]. It is notable that amongst both children and adults, EoE mainly afflicts males with a male to female ratio of approximately 3 : 1 in most series [1, 25].

The distinction between adult and paediatric EoE may relate to the increased recognition of the condition, rather than two rigidly distinct entities. In other words, in the past, paediatric cases may have been missed and are now being diagnosed in adulthood. A recent prospective study suggests this is the case, demonstrating that EoE in more than 70% of paediatric cases remains active on transition to young adulthood over a period of 5 years' observation [26]. The authors suggest that both paediatric- and adult-onset conditions exist (as is the case with asthma), but that a significant number of current paediatric-onset cases will progress to adulthood in what is increasingly viewed as a chronic condition.

The male predominance of EoE is unique when compared to other apparently related conditions, such as asthma, atopic dermatitis and seasonal rhinitis, that share key similarities such as the eosinophilic infiltrate and atopy defined as an elevated IgE to common food or environmental allergens [17, 27, 28]. Classical food allergy (characterised by anaphylaxis or angioedema within minutes to hours of food ingestion) demonstrates a male predominance in early life that disappears or even slightly favours females in adulthood according to some studies [17]. Asthma again shows a male predominance in childhood that disappears later in favour of females [28]. Finally, atopic dermatitis favours females in both children and adults [27].

Thymic stromal lymphopoietin (TSLP) is a cytokine produced by epithelial cells that is central to the pathogenesis of EoE, as demonstrated by animal models and recent human studies [6, 9, 29]. Intriguingly, the gene coding for the TSLP receptor (TSLP – R, that is, cytokine receptor – like factor 2 – CRLF2) is found on a pseudo-autosomal region of the X and Y chromosomes (Xp22.3 and Yp 11.3), and statistical analysis has demonstrated that a single nucleotide polymorphism of this region predisposes male patients to develop EoE [6]. Furthermore, a SNP in the region coding TSLP itself (5q 22.1) predisposes to EoE [6]. Thus, TSLP-related inflammatory pathways may in part contribute to the gender predominance.

Other factors related to gender predominance can be considered, but remain unstudied. First, mitochondrial DNA is inherited from the mother, and it is notable that mitochondrial dysfunction has been attributed to result from allergen exposure in an animal airways model [3]. Furthermore, a maternal history of atopy may predispose to asthma to a greater extent than a paternal one, and a SNP in a region of mitochondrial DNA has been linked to elevated IgE levels and atopy [3]. Secondly, relaxin is a hormone present in large amounts in pregnancy, in small amounts in non-pregnant females of reproductive age and possibly also in males [30]. It may have the potential to decrease fibrosis in a range of organs, as demonstrated by animal models [31]. It is acknowledged that most patients with EoE never become pregnant (many paediatric patients and a male predominance in adulthood). A study of relaxin in human bronchial biopsies suggests an association with the remodelling process in asthma, whilst a greater expression of relaxin receptors in female compared with male cruciate ligament tissue has been cited as an explanation for greater tissue laxity in females [32]. Further research may allow the therapeutic use of relaxin in the future.

SNPs unrelated to gender have been implicated as risk factors for EoE [33]. Eotaxin-3, a cytokine expressed by epithelium, plays a central role in eosinophil recruitment

to the oesophagus, and a SNP (+2496 GG on chromosome 7) correlates with EoE development [34]. A SNP coding for filaggrin, an epithelial structural protein, has also been implicated in EoE, whilst a SNP coding for TGF correlates with response to inhaled corticosteroids (see below) [35, 36]. Gene expression studies have also detailed a 'genetic signature or thumbprint' of EoE, useful in differentiating this condition from the more common GERD, although arguably such research may document the response to inflammation as opposed to causative sequences [10].

The timing and nature of food and aeroallergen exposures

The dominant theory pertaining to the likely pathogenesis of EoE is that food antigens are causative [37]. The use of an elemental diet can eliminate eosinophilic infiltration in the oesophagus in up to 90% of children and 75% of adults, and the less restrictive six-food elimination diet is successful in approximately 65% of adults and children [1]. Gonsalves *et al.* [24] not only demonstrated endoscopic and histological recurrence of the condition following successful treatment with the six-food elimination diet, but also histological and in many cases observable endoscopic recurrence after reintroduction of the putative foods.

EoE can be viewed as a form of food allergy with distinct features, lacking the acute 'allergic' features (anaphylaxis or angioedema characteristic of classical food allergy or oral food allergy syndrome) but sharing the atopic profile of the sufferers (that is elevation in serum IgE to aero and/or food allergens, and frequent co-morbid atopic conditions such as asthma or rhinitis) [38]. As food allergy may be considered a defect of immune tolerance, and antigen exposure is a factor in the development of tolerance, the timing and magnitude of antigen exposure in shaping the immune system (e.g. the type of extent of food and aeroallergen exposure) may be important in disease pathogenesis.

Much ongoing research is dedicated to factors influencing sensitisation and tolerance to food antigens with reference to classical IgE-mediated food allergy [17]. This may be of relevance to EoE, particularly given the observed increase in incidence over time (see below). For several decades, allergy-prevention guidelines have stressed late introduction of food antigens to infants. However, food allergy amongst children has increased during this period. Animal models have since suggested that both oral and cutaneous exposure to antigens in early life may be integral to achieving immune tolerance [17]. As a result, guidelines issued in the last few years have advocated cautious exposure to a wide range of foods from 4 months of age, whilst maintaining breastfeeding as the primary source of nutrition

[39]. Breastfeeding during the first 6 months of life may decrease the risk of food allergies, although the mechanisms have not been delineated [39]. Also, the use of acid-suppressing medication may increase food allergen sensitisation, possibly by decreasing protein degradation of food antigens and increasing intestinal exposure to intact antigens [40].

It has also been proposed that aeroallergens may cause or contribute to the pathogenesis of EoE. The supportive data are limited to uncontrolled observational studies and an animal model. Case reports detail sudden symptomatic worsening following seasonal aeroallergen exposure, and sublingual immunotherapy has been hypothesised to both cause (precede the diagnosis) and cure (disappearance of EoE following the treatment of rhinitis) the condition [41–43]. Mishra *et al.* [44] showed that ovalbumin-sensitised mice developed oesophageal eosinophilia in response to airway but not gastrointestinal rechallenge. Almansa *et al.* [45] and Moawad *et al.* both demonstrated a seasonal peak of EoE diagnosed at gastroscopy. The assertion of these studies is that patients with EoE present in spring/summer when aeroallergens are at their peak atmospheric concentration. Notable weaknesses of both studies are the lack of a control group and the fact that the case definition included all-comers (i.e. both newly diagnosed and past cases). Both were also retrospective and, hence, susceptible to recall bias.

In an attempt to address some of the methodological issues related to the study of potential seasonality in presentation of EoE, our group performed a retrospective study of all food bolus obstruction episodes occurring across six metropolitan hospitals over a period of 10 years. As food bolus obstruction events (FBOEs) are one of the key clinical features of EoE, and as FBOEs are caused by EoE or GERD in similar proportion, a control group as such (i.e. GERD) is hence included. In this study of 1082 individuals, cases of GERD and EoE were both evenly distributed across the year. Thus, amongst the 88 patients who were diagnosed with EoE, the FBOEs were evenly distributed throughout the year. Again, the notable weaknesses are the retrospective nature of data collection. Also, disappointingly, few patients (5–45%) underwent biopsies at gastroscopy [46].

The role of aeroallergens in EoE pathogenesis may foreseeably be as a cofactor in some or many patients, with food antigens playing a more dominant role. The ability of an elemental diet to induce complete histological remission in a majority supports this assertion. As many patients with EoE have coexistent atopic disease (especially seasonal rhinitis), it is also possible that seasonal worsening of that disease may contribute to EoE by facilitating secondary trafficking of eosinophils to the oesophagus. This has been demonstrated both in the research setting, where exposure of the bronchioles

to aeroallergens at the time of bronchoscopy can induce nasal mucosal eosinophilia, and clinically in relation to the control of asthma and rhinitis [47, 48]. The 'common airway' hypothesis asserts that control of rhinitis improves asthma therapy.

Geographical disparity in the prevalence of EoE has been suggested by a retrospective epidemiological study examining climatic regions in North America [49]. Arid/temperate zones manifested higher rates of diagnosis of EoE on endoscopic biopsy. Tropical regions manifested the fewer relative diagnoses of EoE, using total cases undergoing oesophageal biopsy as the reference [49]. The reason for a geographical disparity is not known, but could include variations in atmospheric pollen counts, which are higher in low humidity zones, and/or regions where putative tree or grass pollens are abundant. Alternatively, the role of serum vitamin D levels has been proposed as a protective factor in tropical environments in atopic conditions per se, using adrenaline auto-injectors or hospital admissions for anaphylaxis as a surrogate marker [50]. It is notable that conflicting data concerning the geographical influence on atopy exist; a recent Australian study demonstrated that distance away from the equator and, therefore, sunlight actually predisposes to atopy [51]. Much remains to be clarified.

The effects of migration on the development of EoE have not been explored. Migration between countries

and climate zones has been proposed as a factor influencing the development and severity of other atopic conditions, particularly rhinitis. Asian immigrants to Melbourne, Australia were observed to develop asthma more commonly than Australian-born non-Asian and Australian-born Asian populations [52]. The length of stay positively correlated with the likelihood of symptom development. The new occurrence of rhinitis amongst children who had migrated to Italy also correlated with the length of time living in the new region. We have observed in our own patient group of adult patients a disproportionately large number who have migrated from overseas in young adulthood. The scientific validity of this observation cannot be asserted; however, it is conceivable that exposure to novel (to the migrant) region-specific aero or food allergens may precipitate the disease. Further study seems warranted.

Barrier function and microbiota

Impairments in the structural integrity of the oesophageal mucosal barrier may predispose to and/or perpetuate EoE. Research focussed on EoE directly is lacking, but much attention and importance have been placed on variations in epithelial barrier function in patients with atopic dermatitis. Filaggrin is a structural protein of critical importance in the development of dermatitis. In health, filaggrin is found in the stratum corneum

Established risk factors for EoE

Risk factor	Proposed Mechanism/s
Male gender	TSLP on sex chromosomes [29], Relaxin* [73]
Caucasian	Non-X linked SNP's, e.g. for Filaggrin, Eotaxin 3 [35]
Atopy	IgE-mediated inflammatory infiltration [25]

Putative risk factors for EoE

Risk factor	Proposed Mechanism/s
Impaired barrier function (may due to GORD, be genetic, e.g. filaggrin, or due to altered microbiota)	Increased antigen exposure to oesophageal mucosa [20]
Aeroallergens in spring/summer	Exposure of air passages leading to an inflammatory reaction and trafficking of eosinophils to the oesophagus [33]
Impaired tolerance to food antigens*	Immune reaction may be increased in infants not exposed to a wide range of foods, in those born by C section [74]
Commercially prepared foods*	Agglutinated proteins incite immune reaction [21]
Proton pump inhibitor use	Gastric pH is higher, and hence, proteins are not denatured and greater antigen exposure may results [59]
Migration as an adult*	Novel antigens incite immune reaction
Increased fibrotic remodelling	Decreased relaxin expression, SNP's for TGF B, SNP's for ACE [32, 66]
Living in a temperate or arid climate	Low vitamin D levels and/or higher aeroallergen exposures [75]

*Hypothesis generated from other related disease processes or anecdotal observation.

and binds keratin and intermediate filaments [11]. The gene for pro-filaggrin, which is subsequently phosphorylated to filaggrin, is located on chromosome 1. Specific mutations within this locus have been described to cause or greatly increase the risk of ichthyosis vulgaris and, of great relevance to EoE, atopic dermatitis [11]. As human skin is composed of stratified squamous keratinising epithelium, the importance of filaggrin in keratin attachment is apparent. However, the squamous epithelium of the oesophagus does not undergo keratinisation to a significant extent. Yet, both of these conditions, along with asthma, correlate with an SNP coding for filaggrin (R501X and 2282 del4), albeit to a lesser extent in the case of asthma and EoE [53, 54]. Blanchard demonstrated that whilst SNPs for filaggrin correlated with the development of EoE (independent of the risk of atopic dermatitis), that filaggrin expression measured by mRNA analysis was decreased in all patients, and was influenced by interleukin-13 production. Hence, it remains to be seen if the association between filaggrin and EoE is more than a confounding factor, simply demonstrating the coexistence of EoE with atopic dermatitis, or occurring as a secondary response to eosinophilic inflammation, or if instead there is a hitherto unknown role for filaggrin in the oesophagus that contributes to the pathogenesis of EoE. The evidence thus far suggests that filaggrin is not of central importance in EoE as immunohistochemical staining of the oesophagus has failed to reveal filaggrin expression [11].

Proteins aside from filaggrin, such as occludins, claudins and cadherins, may be important in EoE. Patients with atopic dermatitis have demonstrable decreases in the production of tight junction proteins, claudin-1 and claudin-23 [55]. Furthermore, single nucleotide polymorphisms in claudin-1 have been demonstrated in patients with AD, implying that decreased protein expression results in disease, rather than being a result of the dermatitis [55]. A deficiency of the cadherin desmoglein 1 may result in impaired barrier integrity in patients with EoE, and the expression of desmoglein 1 is influenced by interleukin 13, that is, in turn commonly elevated in this patient group [56]. Patients with connective tissue disease have been noted to have an eightfold increase in prevalence of EoE, the cause unknown, but conceivably could relate to barrier function or may relate to allergic inflammation (see TGF- β). It is interesting to note that disruption of tight junction proteins is thought to contribute to the increase in size of intracellular spaces in patients with GERD and that treating patients with EoE using proton pump inhibitors improves the histology in many patients and is considered a first-line therapy [57, 58]. It could be hypothesised that GERD may cause or precipitate EoE [59]. Abnormalities in tight junction protein and hence barrier function warrant further study.

Microbiota of the oesophagus and possible effects on barrier function and immune tolerance may be important in the pathogenesis of EoE. Limited studies in patients with GERD, Barrett's oesophagus and oesophageal adenocarcinoma have reported a decrease in the microbial diversity in these diseases, with a propensity to be colonised with *Clostridium consisus* in one study [60, 61]. It is not known if the difference in microbial diversity represents a causal role for some bacteria, or rather a secondary change to altered local conditions. Little is known about the microbial profile in patients with EoE.

Microbiota of the large intestine (and presumably the oesophagus) is established in the days and weeks following delivery of the infant and may influence the development of food allergy [62]. Children born via caesarean section and those administered probiotics in the first 6 months of life may have a lower rate of food allergy [17]. Bacterial colonisation of the skin is important in atopic dermatitis, with different populations in those with the condition compared with healthy controls and demonstrable improvement with antibiotics in some patients [63]. Defensins are proteins that are secreted at the mucosal surface and play a role in maintaining microbial homeostasis, being considered part of the innate immune system. It has been noted that patients with atopic dermatitis and, more recently, those with EoE have a decreased expression of defensins (using techniques *in vitro*) [64]. Further, studies *in vivo* appear warranted.

Are all cases of EoE the same? – Fibrosis and stricture formation

A key question in managing any chronic illness is prognostic evaluation, counselling and (potentially) appropriate management selection. A spectrum of clinical, endoscopic and histological pictures emerges across patients with the condition, including those with recurrent, frequent food bolus obstruction, those with severe oesophageal narrowing limiting scope passage and those with variable eosinophil counts or lamina propria thickness at biopsy [15, 65]. To date, neither the endoscopic appearance nor the eosinophil counts have been predictive of symptom severity or response to therapy [66, 67]. Notably, the diagnostic validity of endoscopic visualisation alone (in the absence of biopsy) in diagnosis is poor. Furthermore, the absolute eosinophil count does not correlate with symptom severity as measured by questionnaire [1]. Schoepfer in a retrospective study of 200 patients demonstrated increased stricture formation in those patients whose diagnosis was delayed; for example, 17% had strictures that were diagnosed within 2 years of the onset of symptoms, compared with > 60% when the diagnosis was delayed > 14 years [69]. Hence, it is apparent that diagnosis (and presumably treatment) alters the natural history of the condition.

Moreover, a mandate to treat patients not only to alleviate symptoms but also to avoid future pathological oesophageal narrowing is present. Current first-line treatments for EoE include swallowed corticosteroids (dry powder or gel) as well as dietary therapy. Short-term prospective studies have shown that both may result in a complete or near complete disappearance of eosinophils and reduction in epithelial as well as lamina propria thickness [1, 24, 36]. It is logical to assume that maintenance of these therapies will alleviate symptoms and minimise stricture formation long term, although data are not yet forthcoming.

The search for prognostic variables that will predict severe progression with stricture formation or response to treatment is a worthy research goal. Aceves et al. demonstrated that oesophageal remodelling in EoE was reversed with topical steroids in some patients and that a SNP coding for TGF- β (19q13) predicted treatment response in this group [9, 70]. It has also been observed that TGF- β receptor (9q 22) mutations occur in the childhood-onset Loews Dietz syndrome (characterised by high IgE levels, multiple atopic conditions and eosinophilia including the gastrointestinal tract) suggesting that mutations in this receptor may strongly predispose to human atopic conditions, and demonstrating the complexity of the relationship between allergic inflammation and mediators thought to promote fibrosis [71]. Furthermore, Abonia et al. [68] demonstrated TGF- β expression by mast cells and eosinophils again highlighting this complexity. It is conceivable that such an approach correlating genetic alterations in terms of key

pathological processes of inflammation and fibrosis and response to therapy may result in improved understanding and therapeutic advances. Polymorphisms in the angiotensin converting enzyme (ACE) gene (17q 22.3 – more than a dozen mutations noted), already implicated in cardiovascular disease and pulmonary fibrosis, are one such example [72]. Already, human trials on the angiotensin 2 receptor antagonist (losartan) in the treatment of EoE have commenced.

Conclusion

EoE is disease that presents with dysphagia and/or food bolus obstruction events. Gender (male), race (Caucasian) and atopy confer increased risk. The elemental diet and to a lesser extent the six-food elimination diet result in complete remission in many, implying that food antigens are causative. The timing and nature of food antigen exposure may be important in inducing or reversing immune tolerance and may explain the apparent increasing incidence of the condition. Aeroallergens may play a role. Oesophageal barrier function, microbiota and the clarification of factors influencing fibrous remodelling appear important areas for future study and understanding of this newly recognised condition.

Conflict of interest

The authors declare no conflict of interest.

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