

EOSINOPHILIC OESOPHAGITIS

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ABSTRACT

Eosinophilic oesophagitis is a chronic immune/antigen-mediated disease defined by eosinophilic inflammation of the oesophagus and by symptoms of oesophageal dysfunction. The disease is sometimes referred to as 'asthma of the oesophagus' because of its similar clinical and pathological characteristics to asthma. It is currently the most prevalent cause of oesophagitis after gastro-oesophageal reflux disease. The aetiology of eosinophilic oesophagitis is multifactorial and includes environmental triggers, early-life influences and genetic predisposition. This is a complex condition and the pathogenesis is still not completely clear. Presentation varies according to age, evolving from non-specific symptoms in the very young population to more specific oesophageal symptoms such as dysphagia in the older age group. Clinical suspicion should always be followed by upper gastrointestinal endoscopy and biopsies confirming oesophageal eosinophilia. Multidisciplinary management is key and should include paediatricians, gastroenterologists, dietitians, allergists and pathologists. With this article I aim to raise awareness of this condition in order to encourage earlier recognition and treatment.

Keywords: eosinophilic oesophagitis; eosinophilic inflammation; oesophagus; oesophageal dysfunction

INTRODUCTION

Eosinophilic oesophagitis (EOE) is characterised by symptoms of oesophageal dysfunction, histologically by > 15 eosinophils per high power field (eos/hpf); it is a disease isolated to the oesophagus only. It is sometimes referred to as the 'asthma of the oesophagus' because of its similar clinical and pathological characteristics with asthma.¹ Patients suffering from EOE experience a significant decrease in quality of life (QoL) as a result of food-related symptoms. No risk associated with malignancy or increased mortality has been identified.²

Initial guidelines published in 2007 concluded that gastro-oesophageal reflux disease (GORD) and EOE were thought to be mutually exclusive diseases. To differentiate between the two conditions expert consensus determined that inflammation related to GORD could be ruled out with high-dose proton pump inhibitor (PPI) treatment for 6–8 weeks or with a pH-impedance monitor. In the latest 2018 guidelines a new condition termed PPI – responsive oesophageal eosinophilia (PPI-REE) was published.³ PPI-REE patients have symptoms of oesophageal dysfunction and more than 15 eos/hpf; however, clinical presentation is not consistent with GORD. Evidence from a number of studies now suggests that EOE and GORD are not mutually exclusive and in fact may share a complex relationship.^{4–7} They can coexist: EOE can lead to secondary reflux owing to oesophageal dysmotility, and GORD can lead to decreased barrier integrity, allowing allergen exposure and subsequent EOE.⁸

INCIDENCE

Since the discovery of this condition in the 1990s, its incidence has escalated. Previously considered a rare disorder, EOE is increasingly being reported in different regions across the globe, including Australia, North and South America, Europe, Asia and the Middle East. A recent 20-year prospective study in Switzerland has revealed a true increase in incidence and not just increased recognition by gastroenterologists and pathologists.⁸ The incidence is estimated at 10.4 per 10 000 population in children and 3.0 per 10 000 population in adults. The true incidence and prevalence of EOE is probably underestimated as only patients who warranted biopsies were included in the studies.^{10,11,12}

PATHOGENESIS OF EOE

The pathogenesis of EOE results from complex interactions between environmental triggers, early-life influences and genetics.

ENVIRONMENTAL FACTORS

Unlike immune-mediated diseases, EOE is a T-helper, type-2 cell predominant inflammatory process triggered by allergens. Children and young adolescents present predominantly with a disease driven by food antigens, whereas adults experience environmental sensitisation too.

Notably, up to 80% of patients with EOE have associated atopic conditions, asthma, allergic rhinitis (AR) or known food allergies.¹² As a result, the latest consensus conference on EOE recommends an evaluation by an allergist or an

immunologist. Immediate-type, food-allergy testing is warranted to identify comorbid food-induced allergies in EOE patients. Both serum IgE and skin-prick testing (SPT) for aero-allergens are recommended. SPTs, however, predict only 13% of food associations detected by elimination diets. Based on elimination diets and reintroduction tests, wheat and milk were the most common allergens.¹³

GENETIC PREDISPOSITION

Genetic epidemiology studies in families suggest that genetics plays a role, but EOE does not follow the classic Mendelian inheritance pattern. Monozygotic twins show a 41% concordance for the trait, whereas dizygotic twins have a 21% concordance. A risk of 2.4% is reported in unaffected families.¹¹

First-degree relatives of patients with EOE have an increased propensity for developing auto-immune conditions, including Coeliac disease, Crohn's disease, rheumatoid arthritis, ulcerative colitis, IgA deficiency, common variable immune deficiency (CVID), multiple sclerosis and Hashimoto's thyroiditis.¹⁴

EOE is described in all age groups but predominantly affects white males, with onset occurring from school age to midlife. Other ethnicities affected include Asians, Americans, Latin-Americans and Africans. Most studies have found that the male sex has a 3 : 1 preponderance, and a family history of EOE is often reported, with the heritability risk estimated to be 2%.¹⁵ Taking a thorough family history is therefore an essential part of the assessment of EOE and may help to make a timely diagnosis.

Genome-wide association studies have identified genetic variants predisposing to EOE on chromosome 5q22 (TSLP gene) and 2p23 (CAPN14 gene). A link was also identified between EOE and Eotaxin-3, a gene encoding an eosinophil-specific chemoattractant.^{16,17}

EARLY-LIFE INFLUENCES

Early-life factors such as maternal fever, pre-term labour, Caesarean deliveries, antibiotic exposure during infancy, a lack of breastfeeding and living in a lower-density population area have all been associated with an increased risk of EOE.¹⁸ The inverse is true for exposure to smoking in early life as this seems to have a protective effect with regard to the development of EOE.

This may imply that altered stimulation of the immune system at an early age may predispose individuals to the development of

EOE. A lack of exposure to microbes and an altered microbiome profile also may play a role, as it does for atopic diseases such as asthma and atopic dermatitis (AD).^{19,20}

CLINICAL ASPECTS AND DIAGNOSIS

Clinical experience and research suggest that different clinical phenotypes may exist. Oesophageal strictures may be more prone to developing in some patients and families as opposed to other families. Some patients may respond to dietary intervention alone and others will require additional medical therapy. Symptoms develop at any age but are often recognised as soon as early childhood. Some patients experience intermittent symptoms and others constantly. Presentation varies according to age, evolving from non-specific symptoms in the very young population (GORD and feeding problems) to more specific oesophageal symptoms such as dysphagia in the older age group. Some patients experience only gastro-oesophageal reflux symptoms and oesophageal discomfort. In such cases the symptoms are usually refractory to standard GORD treatment and therefore warrant further investigation.¹⁵

Patients also develop compensatory mechanisms to overcome the challenges they face. A young child with symptoms may avoid certain foods; meals may take excessively long, thanks to the slow chewing of food, and copious amounts of water or sauces are used together with their food.^{21,22} Table I summarises the spectrum of symptoms experienced according to age group. Table II lists questions proposed as part of the medical evaluation.

Clinical suspicion should always be followed by upper gastrointestinal endoscopy and biopsies confirming oesophageal eosinophilia. The following diagnostic criteria are required for diagnosis:

- symptoms of oesophageal dysfunction;
- eosinophilic oesophageal inflammation > 15 eos/hpf affecting the oesophagus alone, and
- exclusion of other conditions with oesophageal eosinophilia.^{13,17}

TABLE II: QUESTIONS TO INCLUDE IN MEDICAL HISTORY

1. Do you chew your food a lot?
2. Are you always the last to finish during mealtimes?
3. Does food tend to 'get stuck' in your throat?
4. Do you drink plenty of water during mealtimes to help you swallow your food?
5. Do you put a lot of sauces on your food to help you swallow your food?
6. Do you avoid certain foods such as meat, rice or bread?
7. Do you cut your food into very small pieces?
8. Do you have a family member with similar symptoms?

TABLE I: PRESENTING SYMPTOMS AND SIGNS ACCORDING TO AGE GROUP

PRE-SCHOOLERS	SCHOOL-AGE CHILDREN	OLDER CHILDREN/ ADOLESCENTS	ADULTS
Refusal to try new foods Intake of smaller amount than appropriate for age Vomiting or regurgitation Irritability Abdominal pain Weight loss or failure to thrive	Food refusal Preference for soft and liquid diet "Slow eaters" Flushing down bolus of food with fluid Abdominal pain Vomiting	Preference for soft diet Choking or gagging Dysphagia May show fear or anxiety during mealtimes Impaction of food	Dysphagia Heartburn Chest pain Impaction of food Rarely spontaneous oesophageal perforation

Table III lists other conditions to be excluded.

TABLE III: OTHER CONDITIONS WITH EOSOPHAGEAL EOSINOPHILIA TO BE EXCLUDED

GORD	Infection
Eosinophilic gastroenteritis	Hyperoesinophilic syndrome
Coeliac disease	Achalasia
Crohn's disease	Drug hypersensitivity
Connective tissue disease	Vasculitis
Graft vs Host disease	Pemphigoid vegetans

Misdiagnosis of a Schatzki ring or GORD in adults is common and only delays the diagnosis of EOE. Patients are often subjected to repeated endoscopies, balloon dilatations and inappropriate therapies before EOE is finally diagnosed.

Upper gastrointestinal endoscopy performed includes inspection and biopsies of the oesophagus, stomach and duodenum (to exclude alternative pathology). Recommendations are to take up to six biopsies in the oesophagus, typically from the proximal and distal parts. Histological features confirming diagnosis of EOE include trachealisation (fixed eosinophilic concentric rings), 'furrowing' (longitudinal rings or furrows), white exudate/spots, fragile oesophageal mucosa ('crepe paper mucosa'), pale oesophageal mucosa with decreased vascularity and a narrow calibre oesophagus.²³ (See Figure 1.)

These findings are not pathognomic of EOE and cannot be used as a basis for treatment decisions. White exudate/spots may be mistaken for candidal oesophagitis and pale oesophagus with decreased vascularity with GORD. Oesophageal rings and stenosis are much more common in the adult population; they are seen in only 25% of children. Biopsies must always be performed, because inspection will reveal a normal oesophageal mucosa in up to 30% of children and 10% of adults.²⁴

TREATMENT

Untreated EOE in children will progress to subepithelial fibrosis in adulthood and although this is not life-threatening, it may cause permanent damage to the oesophagus. The treatment of EOE should commence with two goals in mind: the first is to resolve symptoms and hence improve QoL; the second is to prevent the progression of inflammation and damage resulting from tissue remodelling. EOE is a chronic inflammatory condition and therefore long-term follow-up and adherence are crucial. Ensuring optimal growth and development in children is a priority.

The three pillars of treatment are diet, drugs and dilatation ('the 3 Ds'). The first two act on inflammation and the last on established fibrosis. The approach towards EOE patients should be individualised according to the patient's clinical assessment, their concerns and family dynamics, and might be interchangeable over time.²⁵ Team evaluation should include a paediatric gastroenterologist or gastroenterologist, a dietitian skilled in EOE and an allergist. The dietitian ensures that the caloric, electrolyte and micronutrient intake during elimination diets is adequate. The aim should be to identify food triggers in order to avoid them and to maintain remission without the need for additional drugs, if possible.



A: Eosinophilic abscesses



B: Trachealisation (concentric rings)



C: Linear furrowing



D: Food impaction

Figure 1: Images from personal archive

ELIMINATION DIET

Three possible strategies include an elemental diet (ED), an allergy testing-based elimination diet (ATBD) and an empiric elimination of food triggers that includes the six-food elimination diet (SFED), the four-food elimination diet (FFED) and the two-food elimination diet (TFED). Evaluating for clinical and histological response to a specific diet can be achieved only with repeated endoscopies: the first endoscopy should be before the initiation of the diet; the second biopsy after six weeks of an elimination diet. If remission is achieved, the sequential reintroduction of eliminated foods will take place with endoscopies performed in between. Once a food trigger is identified, it is permanently eliminated from the diet.

This approach is very cumbersome and inconvenient for most patients, especially children, as it involves multiple endoscopies. Adherence can be challenging; therefore proper education regarding the treatment plan is essential. Patients need to realise that elimination diets are not extensive in most cases and are short term, usually lasting only until the offending triggers are identified.⁶

DRUGS

Drugs include acid suppressive medication such as PPIs and corticosteroids (CS). A first step could constitute the initiation of PPIs because these drugs are considered safe and up to 50% of patients will achieve remission. These patients are known to have Proton Pump Inhibitor Responsive Eosinophilic Oesophagitis (PPI-EOE). The reason why some patients respond to PPIs and others do not requires further investigation. Once remission is achieved, dosage should be reduced to as low as possible in order to maintain treatment. Optimal maintenance doses and duration of therapy are not yet well defined and research into these is ongoing.²⁵

Topical corticosteroids have good therapeutic effect; however, they are associated with a higher long-term risk profile. No specific formulary has been developed for EOE specifically, therefore asthma and AR preparations are used. Topical corticosteroids have to be swallowed twice daily and patients should refrain from eating and drinking 30 minutes afterwards. Patients are advised to rinse their mouth after ingestion of medication in order to avoid oral candidiasis. The most commonly used corticosteroids are Fluticasone Propionate and Budesonide: metered-dose inhalers are sprayed and then swallowed. Alternatively, a viscous oral suspension can be

mixed with sucralose, which is swallowed directly. Up to 60% of patients achieve remission. The long-term use of TC has to be monitored for possible complications such as oropharyngeal candidiasis and the suppression of the adrenal axis.²⁶

Systemic corticosteroids (CS) have similar efficacy to topical corticosteroids but they have a more serious side-effect profile. CSs should be used only in emergency situations and only for short periods.¹³

DILATION

Endoscopic dilation is reserved for patients with food impaction and dysphagia where subepithelial fibrosis has been established. The goal of treatment is to achieve an oesophageal lumen suitable for the passage of food. This procedure is 75% effective in patients and the improvement is immediate. This is never used as first-line therapy or monotherapy because it is not at all effective against oesophageal inflammation. The risk of oesophageal perforation is estimated to be less than 1%; this equates to dilation for oesophageal stenosis owing to other aetiologies.²⁷

Other treatments researched include Montelukast, Anti-TNF (Infliximab), Anti-IL5 (Reslizumab), Anti-IgE (Omalizumab).²⁸ None of these has been shown to be effective in improving clinical symptoms and oesophageal eosinophilia. Azathioprine has proved effective, but the side-effects limit the use of this drug.²⁹

CONCLUSION

Although EOE has been recognised as a distinct disease entity for the past two decades, it can no longer be regarded as a rare disorder. The amount of research that has been done and progress that has been made with regard to its pathophysiology, allergy associations, genetic background and new treatment options has been tremendous – and yet there is still so much more to discover. This condition needs to be recognised and early intervention should be a priority.

Multidisciplinary management is key and should include paediatricians, gastroenterologists, dietitians, allergists and pathologists.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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