

Eosinophilic Esophagitis and Allergy

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Key Words

Aeroallergen · Allergy · *Candida albicans* · Eosinophilic esophagitis · Food allergen · IgE

Abstract

Eosinophilic esophagitis (EoE) has been associated with allergic diseases of the airways and skin. Here, we review the current literature on the sensitization pattern of adult EoE patients and critically discuss the diagnostic and therapeutic tools available. Most EoE patients have elevated total IgE levels in serum and are sensitized to aero- and food allergens as assessed by measuring specific IgE levels and/or the skin prick test. Whereas in children with EoE sensitization to food allergens predominate, in adults EoE symptoms do not correlate with IgE sensitization to specific food allergens. However, in two thirds of adult EoE patients, sensitization to cross-reactive plant allergen components have been detected, mainly to profilins and PR10 proteins. So far, food triggering EoE can only be identified by an elimination diet and following reintroduction controlled by endoscopy and histology. Further research is required to elucidate the role of allergens in the pathogenesis of EoE and develop appropriate tools for diagnostic and specific treatment.

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Eosinophilic esophagitis (EoE) has been considered an allergic disease analogous to bronchial asthma and atopic dermatitis [1]. Already the initial papers on EoE report on atopy with increased total IgE levels, blood eosinophilia, and associated allergic airway and/or skin diseases in 70 and 77% of EoE patients, respectively [2, 3]. These observations were confirmed by a more recent study revealing concomitant allergic diseases in 68% of adult EoE patients, with allergic rhinitis (61%) being the most frequent, followed by bronchial asthma (39%) and atopic dermatitis (29%) [4]. Moreover, the characterization of the inflammatory infiltrate and cytokine expression in EoE showed a Th2 inflammatory reaction similar to that of other allergic diseases [5–9]. In addition to eosinophils, high numbers of T cells, B cells, and mast cells were observed as well as strong Th2 cytokine expression in esophageal tissues of EoE patients [5].

Other studies reported seasonal peaks of EoE in parallel with pollen seasons. Over a period of 1 year, significantly more cases of EoE were diagnosed during spring compared with fall and winter, suggesting a potential role of aeroallergens in the pathogenesis of EoE [10, 11]. The seasonal incidence of newly diagnosed EoE was found to correlate with the mean grass pollen counts [11]. Interestingly, according to patient history, the onset of allergic

airway diseases such as allergic rhinitis preceded the manifestation of EoE [4]. Seasonal exacerbations of EoE in spring and summer have been observed in a patient allergic to tree and grass pollen [12]. Moreover, the role of aeroallergens in eliciting EoE has been shown in an experimental animal model [13].

Recent studies have demonstrated sensitization to environmental allergens in 86–93% and to food allergens in 50–82% of adult EoE patients [14, 15]. Investigations using component-resolved diagnostics confirmed these data. Up to 91% of adult EoE patients have an IgE-mediated sensitization to environmental allergens [16]. By measuring serum IgE and applying a skin prick test (SPT), we observed specific IgE to aeroallergens, food allergens or both in 80%, and positive SPT reactions in 84% in a prospective study of 31 adult EoE patients [4]. Sixty-three percent of the patients were sensitized to food allergens, mainly to those cross-reactive with pollen of grass, wheat and rye [4]. Sensitization to milk, egg, fish and seafood was observed in 29% of patients, but was clinically relevant for EoE in only 1 patient [1]. Allergen microarray analysis showed IgE sensitization to species-specific plant and animal aeroallergens in 83%, and to species-specific food allergens in 23% [16]. In 69% of EoE patients, IgE to cross-reactive allergens were detected, namely to cross-reactive plant and animal allergen components in 66 and 9%, respectively [16]. Peanut, soybean, egg white, cow's milk and tree nuts [14], as well as wheat, tomato, carrot and onion [15], were identified as common food allergens in adult EoE patients.

These observations in adult patients are in contrast to the results of pediatric studies. In children, cow's milk, egg and wheat have been identified as causative food allergens by SPTs and patch tests [17]. When these results from adult and pediatric EoE patients are summarized, EoE seems to follow the atopic march describing a decrease of food allergen sensitization but an increase of pollen sensitization and airway allergies in allergic children over time [18]. Indeed, in pediatric EoE populations it was shown that the rate of patients sensitized to food allergens is highest in younger children and decreases afterwards, whereas the rate of sensitization to aeroallergens increased up to 100% in older children and adolescents [19, 20].

In order to tailor an individual and specific treatment, it is important to know whether sensitization to food allergens is relevant for causing and/or eliciting EoE. In our experience, reports on dysphagia after ingestion of meat did not correlate with IgE sensitization to food allergens [16]. Panallergens present in pollen as well as fruits and

vegetables, e.g. profilin, have been identified as relevant allergens in adult EoE [21]. By applying component-resolved diagnostics, we identified profilins and PR10 proteins as the most frequent cross-reactive allergens in adult EoE patients [16]. However, EoE symptoms could not be elicited by double-blind placebo-controlled food challenge tests, and a strict elimination diet of wheat and rye failed to improve EoE symptoms in grass pollen-sensitized patients [22, 23]. Therefore, targeted food elimination diets based on conventional allergen sensitization tests appear to be an unsuccessful approach.

On the other hand, in children with EoE, elimination diets, e.g. six-food elimination diet avoiding milk, wheat, egg, soy, peanut/tree nuts and fish/seafood, as well as an elemental diet, have been shown to be effective in improving symptoms [24, 25]. A recent study in adult EoE patients reported that the six-food elimination diet resulted in a clinical improvement as well as drastic decrease of eosinophil infiltration <10 eosinophils per high-power field in 70% of the patients [26]. Stepwise reintroduction of one food category every 2 weeks under endoscopic and histologic control revealed wheat, milk, soy, nuts and egg as food triggers of EoE [26]. After induction of remission and identification of the responsible trigger by sequential reexposure to foods, a specific elimination diet was shown to maintain disease control over 1 year [27, 28]. Of interest, an elemental diet resulted in a significant decrease of eosinophil infiltration of the esophagus, but failed to improve symptoms and endoscopic signs of EoE in adults [29].

Taken together, adult EoE was shown to be associated with concomitant allergic diseases, elevated total serum IgE levels, IgE sensitization to aeroallergens and cross-reactive plant allergens assessed by measuring specific IgE levels in serum or SPT. However, there is a poor correlation between IgE sensitization to food allergens (specific and cross-reactive) and symptoms of EoE such as dysphagia. A patch test with food allergens has been applied in several studies and for routine diagnostics, but unfortunately, standardized extracts are not available. Double-blind placebo-controlled food challenge failed to elicit EoE in IgE-sensitized patients. Currently, the relevance of certain foods as triggers of EoE can only be proven by a strict elimination diet such as the six-food elimination diet and following reintroduction. However, this procedure has an enormous impact on patient quality of life, requires several endoscopic and histologic examinations, and (as a result) is cost intensive.

In addition to inhalant and food allergens, microbes have been suspected of eliciting EoE. IgE-mediated im-

mune reactions to microbes including *Candida albicans* have been associated with atopic diseases [30]. EoE patients might potentially suffer from a *Candida* infection owing to topical corticosteroid therapy. Indeed, 43% of EoE patients demonstrated IgE specific for *C. albicans* [16]. The incidence in adults exceeded that of pediatric EoE patients (43 vs. 9%), probably due to a longer disease course and/or repeated exposure to corticosteroids [31]. Since swallowed corticosteroids are used for treatment, EoE patients are prone to increased *Candida* colonization and infection of the oral cavity and esophagus [32, 33]. *Candida* was shown to induce the production of IL-5 [34] and, thus, may further contribute to eosinophil accumulation and activation in EoE.

Although EoE has been associated with allergic immune reactions, the exact role of allergens in particular

food proteins in the pathogenesis of EoE remains to be investigated. Understanding these mechanisms might help to develop sensitive and specific diagnostic tools and alternative therapeutic approaches.

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There is no conflict of interest related to this article.

References

- 1 Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I, Schoepfer AM, Simon D, Simon HU: Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012;67:477–490.
- 2 Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vöggtlin J: Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings (in German). *Schweiz Med Wochenschr* 1994;124:1419–1429.
- 3 Vitellas KM, Bennett WF, Bova JG, Johnston JC, Caldwell JH, Mayle JE: Idiopathic eosinophilic esophagitis. *Radiology* 1993;186:789–793.
- 4 Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A: Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol* 2005;115:1090–1092.
- 5 Straumann A, Bauer M, Fischer B, Blaser K, Simon HU: Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954–961.
- 6 Eyerich K, Novak N: Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. *Allergy* 2013;68:974–982.
- 7 Simon HU: Allergic inflammation: focus on eosinophils. *Allergy* 2013;68:823–824.
- 8 Leonardi A, Bogacka E, Fauquert JL, Kowalski ML, Groblewska A, Jedrzejczak-Czechowicz M, Doan S, Marmouz F, Demoly P, Delgado L: Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy* 2012;67:1327–1337.
- 9 Agache I, Akdis C, Jutel M, Virchow JC: Untangling asthma phenotypes and endotypes. *Allergy* 2012;67:835–846.
- 10 Almansa C, Krishna M, Buchner AM, Ghabril MS, Talley N, DeVault KR, Wolfsen H, Raimondo M, Guarderas JC, Achem SR: Seasonal distribution in newly diagnosed cases of eosinophilic esophagitis in adults. *Am J Gastroenterol* 2009;104:828–833.
- 11 Moawad FJ, Veerappan GR, Lake JM, Maydonovitch CL, Haymore BR, Kosisky SE, Wong RK: Correlation between eosinophilic oesophagitis and aeroallergens. *Aliment Pharmacol Ther* 2010;31:509–515.
- 12 Fogg MI, Ruchelli E, Spergel JM: Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol* 2003;112:796–797.
- 13 Mishra A, Hogan SP, Brandt EB, Rothenberg ME: An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83–90.
- 14 Roy-Ghanta S, Larosa DF, Katzka DA: Atopic characteristics of adult patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2008;6:531–535.
- 15 Penfield JD, Lang DM, Goldblum JR, Lopez R, Falk GW: The role of allergy evaluation in adults with eosinophilic esophagitis. *J Clin Gastroenterol* 2010;44:22–27.
- 16 Simon D, Straumann A, Dahinden C, Simon HU: Frequent sensitization to *Candida albicans* and profilins in adult eosinophilic esophagitis. *Allergy* 2013;68:945–948.
- 17 Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA: The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002;109:363–368.
- 18 Wahn U, von Mutius E: Childhood risk factors for atopy and the importance of early intervention. *J Allergy Clin Immunol* 2001;107:567–574.
- 19 Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL, Buckmeier BK, Bullock JZ, Collier AR, Konikoff MR, Noel RJ, Guajardo JR, Rothenberg ME: Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007;119:731–738.
- 20 Sugnam KK, Collins JT, Smith PK, Connor F, Lewindon P, Cleghorn G, Withers G: Dichotomy of food and inhalant allergen sensitization in eosinophilic esophagitis. *Allergy* 2007;62:1257–1260.
- 21 Domínguez-Ortega J, Pérez-Bedmar J, Rodríguez-Jiménez B, Butrón M, Kindelan C, Ledesma A: Eosinophilic esophagitis due to profilin allergy. *J Investig Allergol Clin Immunol* 2009;19:338–339.
- 22 Cochrane SA, Salt LJ, Wantling E, Rogers A, Coutts J, Ballmer-Weber BK, Fritsche P, Fernández-Rivas M, Reig I, Knulst A, Le TM, Asero R, Beyer K, Golding M, Crevel R, Clare Mills EN, Mackie AR: Development of a standardized low-dose double-blind placebo-controlled challenge vehicle for the EuroPrevall project. *Allergy* 2012;67:107–113.
- 23 Simon D, Straumann A, Wenk A, Spichtin H, Simon HU, Braathen LR: Eosinophilic esophagitis in adults – no clinical relevance of wheat and rye sensitizations. *Allergy* 2006;61:1480–1483.
- 24 Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, Melin-Aldana H, Li BU: Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1097–1102.

- 25 Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA: Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503–1512.
- 26 Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I: Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012;142:1451–1459.
- 27 Lucendo AJ, Arias Á, González-Cervera J, Yagüe-Compadre JL, Guagnozzi D, Angueira T, Jiménez-Contreras S, González-Castillo S, Rodríguez-Domínguez B, De Rezende LC, Tenias JM: Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013;131:797–804.
- 28 Lucendo AJ, Arias Á, González-Cervera J, Mota-Huertas T, Yagüe-Compadre JL: Tolerance of a cow's milk-based hydrolyzed formula in patients with eosinophilic esophagitis triggered by milk. *Allergy* 2013;68:1065–1072.
- 29 Peterson KA, Byrne KR, Vinson LA, Ying J, Boynton KK, Fang JC, Gleich GJ, Adler DG, Clayton F: Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol* 2013;108:759–766.
- 30 Kosonen J, Lintu P, Kortekangas-Savolainen O, Kalimo K, Terho EO, Savolainen J: Immediate hypersensitivity to *Malassezia furfur* and *Candida albicans* mannans in vivo and in vitro. *Allergy* 2005;60:238–242.
- 31 Erwin EA, James HR, Gutekunst HM, Russo JM, Kelleher KJ, Platts-Mills TA: Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol* 2010;104:496–502.
- 32 Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel H, Busmann C, Beglinger C, Schoepfer A, Simon HU: Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526–1537.
- 33 Straumann A, Conus S, Degen L, Frei C, Busmann C, Beglinger C, Schoepfer A, Simon HU: Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011;9:400–409.
- 34 Savolainen J, Lintu P, Kosonen J, Kortekangas-Savolainen O, Viander M, Pène J, Kalimo K, Terho EO, Bousquet J: Pityrosporum and Candida specific and non-specific humoral, cellular and cytokine responses in atopic dermatitis patients. *Clin Exp Allergy* 2001;31:125–134.