Oesophageal eosinophilia in children with coeliac disease

Anne Ari,[1,2] Sara Morgenstern,[3,4] Gabriel Chodick,[4] Manar Matar,[1] Ari Silbermintz,[1] Amit Assa,[1,4] Yael Mozer-Glassberg,[1,4] Firas Rinawi,[1] Vered Nachmias-Friedler,[1] Raanan Shamir,[1,4] Noam Zevit[1,4]

[1]Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petach Tikvah, Israel
[2]Pediatrics C, Schneider Children's Medical Center of Israel, Petach Tikvah, Israel
[3]Pathology, Rabin Medical Center, Petach Tikvah, Israel
[4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence to
Dr Noam Zevit, Institute of Gastroenterology, Nutrition, and Liver Diseases, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petach Tikva 49202, Israel; nzevit@gmail.com

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ABSTRACT

Objectives An association between coeliac disease (CD) and eosinophilic oesophagitis (EoE)/oesophageal eosinophilia (EE) has been suggested. We sought to characterise children with CD+EE in-depth and assess the contribution of each condition to the clinical presentation and treatment response.

Study design Medical records of children with both CD+EE, or isolated EoE diagnosed between 2000 and 2014, were retrospectively reviewed and compared with patients with isolated CD or epigastric pain. Frequency of EE was calculated from endoscopy results of patients with suspected CD or epigastric pain between 2011 and 2014. Missing data were obtained via a telephone questionnaire.

Setting Single large, tertiary paediatric centre.

Patients 17 CD+EE, 46 EoE, 302 isolated CD and 247 epigastric pain.

Results The patients with CD+EE shared characteristics of both individual conditions. While age at diagnosis, family history of autoimmunity/CD and anaemia were similar to patients with CD, other characteristics such as male gender, personal/family history of atopy, peripheral eosinophilia and oesophageal white papules were more similar to patients with EoE. Combined patients (CD+EE) tended to present with CD-associated symptoms; the majority (63%) later developed typical EoE symptoms. Only a minority (21%) of combined patients had EE that resolved after a gluten-free diet; another 21% had normalisation of EE upon proton pump inhibitor treatment. The remainder required EoE-specific treatment.

Conclusion Patients with CD found to have EE share characteristics with both isolated CD and EoE. It appears that these are two coexisting entities presenting in the same patient rather than eosinophilia associated with CD, and therefore, interventions separately addressing each condition may be considered.

What is already known on this topic?

- Oesophageal eosinophilia (EE) has been considered a manifestation of coeliac disease (CD).
- Recently, an association between coeliac disease (CD) and EE has been suggested, but inadequately described.

What this study adds?

- EE does not seem to be part of coeliac disease (CD).
- Patients with concomitant CD and EE have characteristics of both individual conditions, without affecting presentation nor disease course of the other; therefore, each entity should be addressed separately.

INTRODUCTION

Eosinophilic oesophagitis (EoE) and coeliac disease (CD) are considered distinct immunological disorders of the gastrointestinal tract. EoE is defined as a clinicopathological entity recognised over two and a half decades ago, and whose prevalence is increasing. The hallmark of EoE is an eosinophil-predominant oesophageal infiltrate. Clinical presentations are age dependent. Infants often present with vomiting, failure to thrive and non-resolving gastro-oesophageal reflux disease (GERD), while older children and adults often present with dysphagia, substernal chest pain and oesophageal food impaction. The majority of patients have coexisting atopy.[1] A diagnosis of EoE currently mandates the presence of symptoms, eosinophil-predominant oesophageal inflammation and lack of response to high-dose proton pump inhibitors (PPIs). When one of these criteria is missing, the term oesophageal eosinophilia (EE) is used. Current treatment options for EoE include dietary interventions or topical oesophageal steroids.[2]

CD is an immune-mediated disorder of the small intestine, induced by ingestion of gluten in genetically susceptible individuals. It appears at any age and is characterised by a wide range of intestinal and extraintestinal manifestations. CD affects at least 1% of children in most countries.[3] The risk of developing atopy among those with CD remains unclear.[4]

Several studies report an association between EE or EoE and CD,[5–12] reporting a prevalence of EE in paediatric patients with CD ranging from 0% to 10%.[6 8–10 13 14] This is markedly higher than the prevalence of EE in the general paediatric population (0.2–43/100 000).[15] Other studies have contended this association in both adults[13 16] and children.[12 17]

CD has often been considered a cause of EE[1]; however, patients with combined EE and CD have not been adequately characterised. It is not known if the eosinophilia in these patients is integral to their

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CD or if these patients have two coexisting immune conditions. While a gluten-free diet (GFD) leads to recovery of CD-associated pathology and symptoms, often there is no improvement of symptoms associated with oesophageal dysfunction.[8 9 18] The primary goal of this study was to characterise paediatric patients with combined CD and EE, and compare them to children with isolated EoE or CD. In addition, we assessed the relative prevalence of EE in our CD cohort when compared with a non-CD high-risk population.

PATIENTS AND METHODS

This was a retrospective cohort study. Patient records from the Institute of Gastroenterology, Nutrition and Liver Diseases at Schneider Children's Medical Center of Israel, a large, tertiary paediatric centre, were searched for patients aged 0–18 years with a diagnosis of EoE, or the combination of EE and CD from January 2000 to November 2014. In addition, records of all patients undergoing upper endoscopy for either suspected CD (based on positive CD serology) or epigastric pain between June 2011 and November 2014 were reviewed. During this time period, routine sampling of oesophageal tissue was performed in patients with both CD and epigastric pain, in contrast to the earlier period when biopsies were taken based on history or endoscopic findings, at the discretion of the endoscopist. Thus, only in the later period could the prevalence of EE in either CD or epigastric pain be assessed.

The last EE+CD files were accessed November 2016 to allow for adequate clinical and laboratory follow-up of combined EE+CD cases. CD was diagnosed in patients having positive CD-associated serology (antitissue transglutaminase, antiendomysial or antideaminated gliadin peptide antibody) and a Marsh score of 2 or greater. EE was defined as ≥15 eosinophils/high power field (eos/hpf), and EoE was diagnosed according to current guidelines.[1 2]

The following data were retrieved for all patients: demographics, ages of diagnosis and onset of symptoms, presenting symptoms, patient and family history of atopic or autoimmune disorders, laboratory findings, endoscopic and pathologic findings. Atopic diseases assessed included: asthma (defined as recurrent wheezing episodes requiring repeated bronchodilator use in children older than 1.5 years and diagnosed by a treating physician/pulmonologist); immunoglobulin E (IgE)-mediated food allergy (diagnosed as a clinical reaction to a food along with either a positive skin prick test, radioallergosorbent test for specific IgE or an oral food challenge, and diagnosed by an allergist); atopic dermatitis (diagnosed by a paediatrician, dermatologist or allergist); and allergic rhinitis (as diagnosed by an allergist). Thrombocytosis was defined as >450 000/mm^3; peripheral eosinophilia as >700 cells/mm^3; anaemia and elevated alanine transaminase (ALT) were defined by age-specific and gender-specific values. A structured telephone questionnaire was used to gather data on atopic and autoimmune conditions in the patient and first-degree relatives, duration of total and exclusive breastfeeding, as well as to inquire of any changes in symptoms since the last follow-up in the clinic.

In this study, differentiation was made between EE and EoE because not all patients had a formal diagnosis of EoE which currently mandates a formal PPI test and clinical symptoms of oesophageal dysfunction. This study was approved by the local institutional review board.

Statistical analysis

Differences in continuous variables with a normal distribution were analysed with Student's t-test, otherwise with Mann-Whitney test. The Fisher's exact χ^2 test was used for categorical variables. Differences were considered significant when $p \leq 0.05$. Tests were adjusted for all pairwise comparisons using the Bonferroni correction. All analyses were conducted using IBM SPSS V.21 (Released 2012. IBM SPSS Statistics for Windows, V.21.0).

RESULTS

Medical records of 612 participants were included, of which 17 were with combined CD+EE, 46 with isolated EoE, 302 with CD and 247 with abdominal pain.

Table 1 summarises patient characteristics.

The patients with combined CD+EE presented at ages similar to the isolated CD group, which were younger than patients with both the epigastric pain and EoE. In contrast, the male preponderance was shared by the combined CD+EE group (65%) and isolated patients with EoE (78%), differing from the CD and epigastric pain groups where females outnumbered males. Neither maximal term of breastfeeding nor months of exclusive breastfeeding differed significantly between the groups.

The presenting symptoms are shown in table 2, the atopic and autoimmune personal/family history in table 3, and the laboratory and endoscopic findings in table 4.

The majority of combined patients presented with symptoms typical of CD including poor weight gain, diarrhoea, short stature and anaemia, and only rarely with EoE-associated symptoms of infancy/early childhood (eg, recurrent vomiting, non-resolving

Table 1 Patient characteristics

	CD+EE+*	CD+EE−†	CD−EoE+‡	EP§	p Value
Age (in years) (range)	5.8 (1.7–8.4)	5.8 (3.6–8.8)	9.2 (±5.6)	13.2 (9.8–15.4)	<0.05¶,**,††
Males, n (%)	11 (64.7%)	109 (36.1%)	36 (78.3%)	82 (33.2%)	<0.05‡‡,§§
SDS height at presentation; median (IQR)	0.6 (−1.5 to 1.4)	−0.4 (−1.3 to −0.4)	0.00 (−1.3 to 0.8)	−0.19 (−0.9 to −0.2)	All NS
SDS weight at presentation; median (IQR)	−0.5 (−1.2 to 0.9)	−0.5 (−1.3 to 0.1)	−0.7 (−1.7 to 0.9)	0.05 (−1.0 to 0.9)	<0.05§§

*CD+EE+, coeliac disease with oesophageal eosinophilia.
†CD+EE−, isolated coeliac disease without oesophageal eosinophilia.
‡CD−EoE+, isolated eosinophilic oesophagitis.
§Epigastric pain.
¶Statistically significant between * and ‡.
**Statistically significant between * and §.
††Statistically significant between † and §.
‡‡Statistically significant between † and ‡.
§§Statistically significant between ‡ and §.
CD, coeliac disease; EE, oesophageal eosinophilia; EoE, eosinophilic oesophagitis; EP, epigastric pain; IQR, interquartile range; NS, non-significant; SDS, standard deviation score.

Table 2 Presenting symptoms

	CD+EE+,* n (%)	CD+EE−,† n (%)	CD−EoE+,‡ n (%)	p Value
Classic coeliac disease symptoms				
Poor weight gain	4 (23.5%)	62 (20.5%)	9 (19.6%)	>0.9
Diarrhoea	3 (17.6%)	44 (14.6%)	0	0.025
Short stature	2 (11.8%)	61 (20.2%)	1 (2.2%)	<0.009§
Anaemia	3 (17.6%)	56 (18.5%)	0	0.007¶,§
Classic EoE symptoms				
Vomiting	2 (11.8%)	15 (5.0%)	13 (28.3%)	<0.001§
Dysphagia	0	0	6 (13.0%)	<0.001¶,§
Food impaction	1 (5.9%)	0	18 (39.1%)	<0.001¶
Strictures	2 (11.8%)	0	15 (32.6%)	<0.001**,§

*CD+EE+, coeliac disease with oesophageal eosinophilia.
†CD+EE−, isolated coeliac disease without oesophageal eosinophilia.
‡CD−EoE+, isolated eosinophilic oesophagitis.
§Statistically significant between † and ‡.
¶Statistically significant between * and ‡.
**Statistically significant between * and †.
CD, coeliac disease; EE, oesophageal eosinophilia; EoE, eosinophilic oesophagitis.

GERD). However, 10/16 (63%) patients with CD+EE developed EoE-associated symptoms such as food impaction (25% vs 0% in patients with CD), dysphagia (44% vs 0% in patients with CD) and recurrent vomiting (25% vs 5% in patients with CD) during their follow-up, as assessed by ongoing patient follow-up/telephone questionnaire in all except one patient who could not be contacted for follow-up.

The isolated CD group and combined CD+EE group were more likely to have autoimmune diseases, including CD, in the family (table 3). In contrast, the personal/family history of atopy in patients with CD+EE was more similar to the patients with EoE than in those with isolated CD.

Combined CD+EE shared the classical laboratory characteristics (table 4) of both the isolated CD group and isolated EoE group. Peripheral eosinophilia appeared more often in patients with combined CD+EE and patients with isolated EoE ($p<0.05$), whereas anaemia tended to be more frequent in both patients with combined CD+EE and isolated CD.

Table 3 History of atopic/autoimmune diseases

	CD+EE+,* n (%)	CD+EE−,† n (%)	CD−EoE+,‡ n (%)	p Value
Asthma	10 (58.8%)	70 (39.8%)	25 (55.6%)	0.001
IgE-mediated food allergy	2 (12.5%)	6 (3.4%)	12 (26.1%)	<0.001§
Atopic dermatitis	7 (43.8%)	40 (23.4%)	13 (28.9%)	0.001
Allergic rhinitis	4 (25%)	21 (12.3%)	13 (28.9%)	0.007§
Any personal history of atopic disease	12 (70.6%)	97 (32.1%)	32 (69.6%)	<0.001¶,§
Any family history of atopic disease	11 (64.7%)	87 (28.8%)	26 (56.6%)	<0.001¶,§
Family history of coeliac disease	4 (25%)	111 (43.7%)	0	<0.001**,§
Family history of autoimmune diseases	8 (47.1%)	105 (47.7%)	9 (20.9%)	<0.001§

*CD+EE+, coeliac disease with oesophageal eosinophilia.
†CD+EE−, isolated coeliac disease without oesophageal eosinophilia.
‡CD−EoE+, isolated eosinophilic oesophagitis.
§Statistically significant between † and ‡.
¶Statistically significant between * and †.
**Statistically significant between * and ‡.
CD, coeliac disease; EE, oesophageal eosinophilia; EoE, eosinophilic oesophagitis; IgE, immunoglobulin E.

Table 4 Laboratory and endoscopy findings

	CD+EE+,* n (%)	CD+EE−,† n (%)	CD−EoE+,‡ n (%)	p Value
Laboratory findings				
Anaemia	6 (37.5%)	100 (35.2%)	6 (13.3%)	<0.001§
Thrombocytosis	1 (6.3%)	38 (13.5%)	2 (4.3%)	<0.001
Eosinophilia	8 (50.0%)	40 (14.2%)	26 (56.5%)	<0.001¶,§
Elevated ALT	1 (6.3%)	19 (7.1%)	1 (2.2%)	0.026
Endoscopy findings				
Normal	5 (29.4%)	287 (95.0%)	4 (8.7%)	<0.001
Furrowed	2 (11.8%)	0	10 (21.7%)	<0.001
Ringed	0	0	5 (10.9%)	<0.001
Strictures	1 (5.9%)	0	1 (2.2%)	<0.001
White papules	6 (35.3%)	5 (1.7%)	17 (37.0%)	<0.001¶,§
Small calibre oesophagus	1 (5.9%)	0	3 (6.5%)	<0.001
Marsh score			–	0.04
2AB	0	1 (0.3%)		
3A	4 (25%)	18 (6.0%)		
3B	4 (25%)	96 (31.9%)		
3C	8 (50%)	186 (61.8%)		
eos/hpf >15 in oesophagus	17 (100%) Mean: 46 SD: 23	0	46 (100%) Mean: 61 SD: 34	<0.001

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†CD+ EE−, isolated coeliac disease without oesophageal eosinophilia.
‡CD−EoE+, isolated eosinophilic oesophagitis.
§Statistically significant between † and ‡.
¶Statistically significant between * and †.
ALT, alanine transaminase; CD, coeliac disease; EE, oesophageal eosinophilia; EoE, eosinophilic oesophagitis; eos, eosinophils; hpf, high power field; SD, standard deviation.

Endoscopic findings (table 4) of patients with combined CD+EE were similar to the isolated EoE group, with presence of white papules reaching significance when compared with patients with CD.

All patients with CD+EE had both conditions diagnosed simultaneously, and none of the patients with CD developed EE after their initial endoscopy.

Outcomes of EE in CD+EE were as follows: 21% (3/14 patients) had EE responsive to a GFD. These patients had a normal appearing oesophagus on both the initial and follow-up endoscopies. The remaining 11 patients had persistent EE on GFD. PPI-responsive EE (PPI-REE) was diagnosed in 21% (3/14). Half of our patients (7/14) were treated with a therapeutic regimen for EoE (topical steroids or further dietary eliminations), 3 of whom had undergone formal PPI challenges. One patient with persistent EE while being on GFD refused any further intervention. Two patients (2/17) were lost to follow-up and one was non-compliant with a GFD and has not yet been reassessed.

All patients presenting between June 2011 and November 2014 with either suspected CD or non-specific epigastric abdominal pain were analysed to determine the prevalence of EE. The prevalence of EE (≥15 eos/hpf) was 11/311 (3.5%) in the suspected CD group as opposed to 7/248 (2.8%) in the patients with abdominal pain ($p=0.81$). However, at a higher eosinophil cut-off (≥30 eos/hpf), the prevalence of EE in patients with CD versus abdominal pain was 9/311 (2.9%) versus 1/248 (0.4%) ($p=0.048$).

DISCUSSION

This study is the first and largest to characterise paediatric patients with combined CD+EE in-depth in comparison with their counterparts with each individual disease. Previous studies were either large epidemiological studies[12 16 17] not structured to analyse individual patient characteristics, or were small case series.[6–10 13 14]

We found that patients with combined CD+EE had typical historical and laboratory findings that would be expected for each of the two conditions separately. While age at diagnosis, family history of autoimmunity, anaemia and CD in family members were similar to patients with CD, other characteristics such as male gender, personal/family history of atopy, peripheral eosinophilia and oesophageal white papules were more similar to patients with EoE. EE did not resolve in the majority of patients with CD+EE while on a GFD, and often patients developed typical EoE-associated symptoms over time. EE was demonstrated in patients with CD and epigastric pain (a high-risk group) at similar frequencies.

In our cohort, patients with combined CD+EE were diagnosed at similar ages as those with isolated CD, and were younger than the four children with combined disease reported by Thompson *et al*.[10] The male preponderance of CD+EE was in concordance with several other reports.[9 12–14]

Autoimmunity, which was recently found to be associated with EoE,[19] was found in family members of 20% of our patients with isolated EoE. However, among the patients with CD+EE, autoimmunity rates among first-degree relatives were higher, similar to patients with isolated CD (47%). Atopic conditions were more frequent in patients with CD+EE (70%) than previously reported (14% (1/7),[8] 50% (3/6),[14] 67% (2/3)),[13] but corresponded to the frequencies expected in EoE. A similar finding was demonstrated for atopy in family members (64% in our patients with CD+EE vs 17% in a previous report of six patients).[6]

White papules, the most common endoscopic oesophageal finding among children with combined CD+EE, were observed in one-third of our cohort in concordance with other studies.[8 9 14]

Our findings suggest that children with combined CD+EE suffer from two coexisting conditions, CD and EE, rather than EE as part of a spectrum of CD-associated findings. This is further supported by our finding that while patients with CD+EE tended to present with symptoms and ages typical of CD, the majority (63%) of these patients later developed EoE-associated symptoms despite GFDs and normalisation of CD-associated serology.

Neither clinical history nor laboratory values adequately discriminated patients with isolated CD from those that would be found to have combined CD+EE. As such, we could not provide a diagnostic algorithm to identify patients with elevated coeliac serology who may need to be screened for EE. Moreover, the EE found in patients with CD is often found in biopsies taken from a normal appearing oesophagus (approximately 30%, as in a previous study[12]). Therefore, it seems reasonable to recommend that patients undergoing endoscopy for suspected CD also undergo an oesophageal biopsy. Current definitions of EoE stipulate clinical symptoms are necessary for a diagnosis of the disease; however, our findings, including the observation that two-thirds of our patients developed EoE-associated symptoms following the identification of EE, seem to indicate that there may be a presymptomatic stage which may be identified, and thus allow for more careful follow-up of these patients. Furthermore, we found that only a minority of patients with CD+EE have resolution of the EE following a prolonged GFD, similar to previous reports[9 10 18] and a meta-analysis.[20] In patients with CD, also diagnosed with EoE who respond to GFDs, wheat may be functioning as the triggering antigen of EoE, a finding that has been reported in 26% of children with EoE.[21]

PPI-REE was diagnosed in 3/14 patients with CD+EE who had not responded to a GFD while 7/14 received standard treatment for EoE. PPI-REE cannot clinically or histologically be differentiated from EoE. In fact, a recent study by Wen *et al*[22] reported overlapping transcriptomes between patients with PPI-REE and those with EoE, but also identified a set of candidate genes to differentiate the two groups. The authors concluded that PPI-REE has significant molecular overlap with EoE, suggesting that PPI-REE may represent a continuum of the allergic mechanisms underlying EoE and thus might constitute a subphenotype of EoE. Furthermore, Molina-Infante *et al*[23] proposed updated diagnostic criteria for EoE in which lack of PPI responsiveness is not mandated for the diagnosis of EoE, but rather is a treatment option for the disease.

In our cohort, EE was similarly frequent in patients with suspected CD and in those with epigastric pain (3.5% and 2.8%, respectively), a finding similar to a recent meta-analysis of paediatric studies that reported a prevalence of EE in children with CD and those undergoing endoscopy for abdominal pain (2.3% and 2.6%, respectively).[15]

This study has several limitations. The retrospective design limits the amount of data available, and, as several physicians with varying clinical protocols have followed different patients, the diagnostic and treatment protocols are not uniform. In addition, 10% of the patients with epigastric pain did not have oesophageal biopsies (all with normal macroscopic appearance of the oesophagus). Nevertheless, we feel that this has not significantly biased the results, because the normal appearing mucosa in these patients would only rarely have eosinophils, as demonstrated by Ludvigsson *et al*[16] in an unselected population of adults. This would thus likely lower the estimation of EE in patients with abdominal pain, making the CD+EE appear comparatively even more significant. Finally, the most recent patient entered in this study was diagnosed in November 2014. This was done purposefully to allow for adequate time to assess for changes in symptoms while on a GFD. As practice management guidelines have not changed in ways that would alter our conclusions, our conclusions are generalisable today.

CONCLUSION

We demonstrate that EE shares a similar frequency between CD and another high-risk group, patients with epigastric pain. Patients who present with combined CD+EE share certain characteristics with their counterparts with isolated CD and other characteristics with their counterparts with EoE. Overall, it appears that EoE is not an element of CD but a separate entity presenting in some patients with CD, and therefore, in such cases, different interventional approaches may be considered. These findings may help future studies delineate the shared or divergent pathways involved in triggering CD and EoE, as well as provoking discussion concerning the diagnosis of early, presymptomatic EoE.

Contributors NZ conceptualised and designed the study, analysed data, drafted the initial manuscript and approved the final manuscript as submitted. AA assisted in designing the study, performed the data acquisition and collection, carried out the analyses, drafted the initial manuscript and approved the final manuscript as submitted. RS conceptualised and designed the study, critically reviewed the manuscript and approved the final manuscript as submitted. SM supervised pathological data collection, reviewed the manuscript and approved

the final manuscript as submitted. GC helped design the study parameters, performed the statistical analyses, reviewed the manuscript and approved the final manuscript as submitted. MM, AS, AA, YMG, FR and VNF assisted in data acquisition, critically reviewed the manuscript and approved the final manuscript as submitted.

Competing interests None declared.

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REFERENCES

1 Liacouras CA, Furuta GT, Hirano I, *et al*. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20.
2 Papadopoulou A, Koletzko S, Heuschkel R, *et al*. Management guidelines of eosinophilic esophagitis in childhood. *J Pediatr Gastroenterol Nutr* 2014;58:107–18.
3 Vriezinga SL, Auricchio R, Bravi E, *et al*. Randomized feeding intervention in infants at high risk for celiac disease. *N Engl J Med* 2014;371:1304–15.
4 Zauli D, Grassi A, Granito A, *et al*. Prevalence of silent coeliac disease in atopics. *Dig Liver Dis* 2000;32:775–9.
5 Pellicano R, De Angelis C, Ribaldone DG, *et al*. 2013 update on celiac disease and eosinophilic esophagitis. *Nutrients* 2013;5:3329–36.
6 Quaglietta L, Coccorullo P, Miele E, *et al*. Eosinophilic oesophagitis and coeliac disease: is there an association? *Aliment Pharmacol Ther* 2007;26:487–93.
7 Kagalwalla AF, Shah A, Ritz S, *et al*. Cow's milk protein-induced eosinophilic esophagitis in a child with gluten-sensitive enteropathy. *J Pediatr Gastroenterol Nutr* 2007;44:386–8.
8 Ooi CY, Day AS, Jackson R, *et al*. Eosinophilic esophagitis in children with celiac disease. *J Gastroenterol Hepatol* 2008;23:1144–8.
9 Leslie C, Mews C, Charles A, *et al*. Celiac disease and eosinophilic esophagitis: a true association. *J Pediatr Gastroenterol Nutr* 2010;50:397–9.
10 Thompson JS, Lebwohl B, Reilly NR, *et al*. Increased incidence of eosinophilic esophagitis in children and adults with celiac disease. *J Clin Gastroenterol* 2012;46:e6–e11.
11 Verzegnassi F, Bua J, De Angelis P, *et al*. Eosinophilic oesophagitis and coeliac disease: is it just a casual association? *Gut* 2007;56:1029–30.
12 Jensen ET, Eluri S, Lebwohl B, *et al*. Increased risk of esophageal eosinophilia and eosinophilic esophagitis in patients with active celiac disease on biopsy. *Clin Gastroenterol Hepatol* 2015;13:1426–31.
13 Stewart MJ, Shaffer E, Urbanski SJ, *et al*. The association between celiac disease and eosinophilic esophagitis in children and adults. *BMC Gastroenterol* 2013;13:96.
14 Dharmaraj R, Hagglund K, Lyons H. Eosinophilic esophagitis associated with celiac disease in children. *BMC Res Notes* 2015;8:263.
15 Soon IS, Butzner JD, Kaplan GG, *et al*. Incidence and prevalence of eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr* 2013;57:72–80.
16 Ludvigsson JF, Aro P, Walker MM, *et al*. Celiac disease, eosinophilic esophagitis and gastroesophageal reflux disease, an adult population-based study. *Scand J Gastroenterol* 2013;48:808–14.
17 Ahmed OI, Qasem SA, Abdulsattar JA, *et al*. Esophageal eosinophilia in pediatric patients with celiac disease: is it a causal or an incidental association? *J Pediatr Gastroenterol Nutr* 2015;60:493–7.
18 Abraham JR, Persad R, Turner JM, *et al*. Gluten-free diet does not appear to induce endoscopic remission of eosinophilic esophagitis in children with coexistent celiac disease. *Can J Gastroenterol* 2012;26:521–4.
19 Peterson K, Firszt R, Fang J, *et al*. Risk of autoimmunity in EoE and families: a population-based cohort study. *Am J Gastroenterol* 2016;111:926–32.
20 Lucendo AJ, Arias Á, Tenias JM. Systematic review: the association between eosinophilic oesophagitis and coeliac disease. *Aliment Pharmacol Ther* 2014;40:422–34.
21 Kagalwalla AF, Shah A, Li BU, *et al*. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr* 2011;53:145–9.
22 Wen T, Dellon ES, Moawad FJ, *et al*. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol* 2015;135:187–97.
23 Molina-Infante J, Bredenoord AJ, Cheng E, *et al*. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut* 2016;65:524–31.

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Notes