Research Article

Role Of Immunoglobulin G4 In Pediatric Eosinophilic Esophagitis: Clinical, Endoscopic And Pathological Study

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Abstract

Background: New studies demonstrate increased oesophageal IgG4 in cases with eosinophilic esophagitis (EoE), proposing a potential IgG4-involved process. The role of IgG4 in pediatric EoE hasn't been widely studied.
Objective: To analyze IgG4 immunohistochemistry staining in oesophageal biopsy specimens of children with EoE in comparison to that of specimens from children with gastroesophageal reflux disease (GERD).
Patients and Methods: In this retrospective study we conducted immunohistochemical staining of IgG4 in oesophageal biopsies from 48 children: Newly diagnosed children with EoE (n = 24), children with reflux oesophagitis (n = 24).
Results: IgG4 presented in higher numbers in plasma cells of eosinophilic esophagitis cases compared to children with GERD (p ≤0.001). Also, IgG4 number in esophageal epithelial cells was significantly higher in EoE cases versus children with GERD (p value≤0.001). Furthermore, there were significant differences regarding IgG4 reaction in extracellular spaces. 23 EoE cases stained positively for IgG4 in extracellular spaces with different intensities of staining (11 weak, 12 strong) whereas only 13 of GERD children stained positively for IgG4 (10 weak, 3 strong). 11 GERD children versus only 1 EoE child showed negative staining for IgG4 in extracellular spaces (p value 0.002).
Conclusions: our study implicates the potential role of IgG4 in esophageal biopsies in children with EoE at diagnosis. Further pediatric studies are needed to confirm this finding which may help to tailor EoE therapies in the future.

Keywords: children, Eosinophilic esophagitis, Gastroesophageal reflux disease, Immunohistochemical analysis of IgG, esophageal biopsies.

Introduction

Eosinophilic gastrointestinal diseases (EGIDs) are uncommon and not completely identified disorders. They defined as the existence of eosinophilic inflammation and distinctive gastrointestinal manifestations (Pesek et al., 2021).
Eosinophilic esophagitis (EOE) is more frequently diagnosed and better identified compared to the non-EoE EGIDs (Quinn et al., 2023). It is a chronic immune disorder of the esophagus. In addition, it is the second most predominant oesophageal disease after GERD (Furuta et al., 2015).
Diagnostic criteria of EOE include: 1) manifestations of oesophageal dysfunction; 2) a maximum oesophageal eosinophil count of at least 15 eos/HPF; 3) exclusion of other potential causes of EOE (Liacouras et al., 2011). Its prevalence is estimated to be 44 to 56 per 100000 subjects in the United States and European nations. EOE cases are more susceptible to atopic disorders, including asthma, eczema, and food allergy (Weidlich et al., 2020).
Eosinophilic Esophagitis pathophysiology is characterized by food antigen-triggered Th2-driven inflammation where eosinophils act as a biomarker and may participate in the occurrence of tissue injury (Quinn et al., 2023). Up to now, EOE has been identified as an IgE-mediated disease. In contrast, this issue is a matter of debate, and recently a correlation with IgG4, but not with IgE, has been recorded (Weidlich et al., 2020). Chronic food antigen exposure can cause IgG4 development in the oesophageal mucosa and allergen binding by IgG4. The role of IgG4 in the development of oesophageal inflammation remains not well-identified (Lim et al., 2021).
Recent studies, both adult and pediatric studies, demonstrate elevated serum and oesophageal IgG4 in cases with EOE, proposing a potential IgG4-involved process (Pope et al., 2019).

Patients and methods

Study design:
A case control study comparing children with EOE with a group of children with GERD of matched age and sex for evaluating immunohistochemistry for IgG4 in esophageal biopsies.

Study Population:
Study groups included: Cases: 24 EOE children aged 1-18 years. The diagnosis of EOE was done according to the diagnostic criteria Of EOE which include: l) manifestations of oesophageal dysfunction; 2) a maximum oesophageal eosinophil count of at least 15 Eos/HPF; 3) exclusion of other potential causes of EOE (Liacouras et al., 2011). The cases were recruited from the gastroenterology and hepatology outpatient clinic in Mansoura University Children's Hospital.
Controls: 24 children with GERD of matched age and sex were comprised in the study.
The controls were recruited from the gastroenterology and hepatology outpatient clinics in Mansoura University Children's Hospital.
Inclusion criteria: Children diagnosed as eosinophilic esophagitis according to the diagnostic criteria of EoE (Liacouras et al., 2011). Exclusion criteria: l. Patient with other causes of esophageal eosinophilia which include GERD, parasitic and fungal infections, inflammatory bowel disease, celiac disease, allergic vasculitis ...etc. 2. Inability to adhere to protocol requirements.

Study methodology:
Both cases and controls had undergone the following:
1. Collection of relevant medical history focusing on:
• Manifestations of oesophageal dysfunction as dysphagia, emesis, heart burn, feeding refusal/aversion and failure to thrive. • History Of atopic diseases. • Family history of atopy.
2. Complete physical examination.
3. Peripheral eosinophil count and percentage.
4. Esophagogastroduodenoscopy (EGD) with a focus on morphologic features of EOE such as attenuation of the sub-epithelial vascular pattern, whitish papules, linear furrows, stacked circular rings, strictures and small calibre esophagus.
5. Endoscopic oesophageal biopsies: at least six oesophageal biopsies were taken from the proximal and distal oesophagus in oesophageal biopsies
6. Detection of IgG4 by Immunohistochemistry or immunofluorescence.

Research ethics
Informed written consents were obtained from all parents of both groups and approved by the

Institutional Research Board of Mansoura Faculty of Medicine, Egypt (MD.24.04.848.R1).

Statistical analysis
Data were analysed using the SPSS program for Windows (version 26). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were defined using number and percent. Continuous variables were presented as mean±SD for normally distributed data and median (Min-Max) for non-normal data. The two groups were compared by independent t test (parametric data) and U test (Non parametric). Spearman correlation was used to correlate continuous variables. Sensitivity and specificity at different cut off points was assessed by ROC curve. The level of significance was set at p-value ≤0.05

Results
Clinical characteristics of the study participants There was an insignificant difference in the age between patients and controls. However, there was a significant difference in gender between both groups, where most of eosinophilic esophagitis cases were males (22 males, 2 females) while GERD patients have nearly equal gender affection (13 males, 11 females).
There were statistically significant differences regarding the main clinical presentations among the cases and control groups. The main clinical presentation among cases was dysphagia (10 out of 24 cases), while only 1 GERD patient presented mainly by dysphagia (p value 0.004). On the other hand, the main clinical presentation among control (GERD) group was nausea and vomiting (16 out of 24) whereas 6 EOE cases present with nausea and vomiting (p value 0.003) Table 1.

Table (1): Main presentations among the study and control groups

Fisher exact test was used, *significant p≤0.05

Main presentations	Study group (no=24)	Control group (no=24)	p value
Age (years) Median (Min-Max)	9.0 (1.20-16.50)	7.50 (2.0-16.0)	0.475
Sex Male Female	22 (91.3%) 2 (8.7%)	13 (52.2%) 11 (47.8%)	0.003*
Dysphagia	10 (41.6%)	1 (4.1%)	0.004*
Food impaction	5 (20.8%)	0 (0.0%)	0.018*
Chocking, gaging	2 (8.3%)	0 (0.0%)	0.489
Reflux, heart burn, chest pain	2 (8. 3%)	2 (8.3%)	1.0
Poor appetite	0 (0.0%)	0 (0.0%)	-
Food aversion	3 (12.5%)	0 (0.0%)	0.233
Weight loss	0 (0.0%)	0 (0.0%)	-
Poor weight gain	0 (0.0%)	0 (0.0%)	-
Nausea, vomiting	6 (25%)	16 (66.6%)	0.003*
Abdominal pain	3 (12.5%)	3 (12.5%)	1.0
Early satiety	1 (4.1%)	0 (0.0%)	1.0
Hematemesis, melena	1 (4.1%)	3 (12.5%)	0.608

Atopic disorders were significantly more common in EOE cases. Statistically significant differences were demonstrated between cases and controls concerning affection by bronchial asthma, eleven cases versus only two controls have bronchial asthma (p=0.003). No statistically significant differences were observed between cases and controls regarding affection by other atopic disorders including atopic dermatitis, allergic rhinitis and food allergy. Also, there was strong family history of atopy among cases compared to controls (p value <0.001). These results are shown in figure 1.

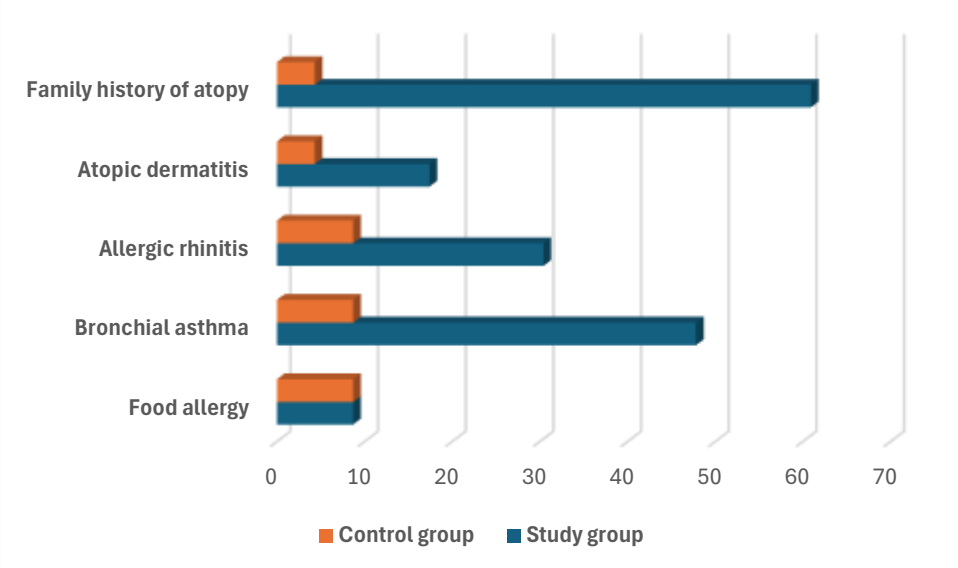

Figure (1): Comorbid health conditions among the study and control groups

Gross endoscopic features:

EoE cases showed variable gross endoscopic features. The most common features were linear furrows (79.2%) and edema (62.5%), followed by exudate (41.6%) and rings (37.5%). Children with GERD showed none of these features. Esophageal stricture was found in four EoE patient versus two GERD patient. On the other side, grossly free endoscopy was found in seven GERD patients versus only one EoE case (p value 0.047). Table 2.

Table (2): Gross endoscopic features among the study and control groups

Gross endoscopic features	Study group (no=24)	Control group (no=24)	p value
Edema	15 (62.5%)	0 (0.0%)	**≤0.001***
Rings	9 (37.5%)	0 (0.0%)	**0.001***
Exudate	10 (41.6%)	0 (0.0%)	**≤0.001***
Furrows	19 (79.2%)	0 (0.0%)	**≤0.001***
Stricture	4 (16.6%)	2 (8.3%)	0.655
Crepe paper mucosa	7 (29.2%)	0 (0.0%)	**0.009***
Grossly free	1 (4.1%)	7 (29.2%)	**0.047***

Immunohistochemical analysis of IgG4 in both cases and controls:

There were statistically significant differences between cases and controls regarding immunohistochemistry (IHC) of IgG4 in esophageal biopsies. IgG4 presented in higher numbers in plasma cells of eosinophilic esophagitis cases compared to children with GERD (p value≤0.001). Also, IgG4 number in esophageal epithelial cells was significantly higher in EoE cases versus children with GERD (p value≤0.001). Also, there was statistically significant differences regarding IgG4 reaction in extracellular spaces. The extracellular IgG4 reaction was seen principally in intercellular location of the squamous epithelium. 23 EoE cases stain positively for IgG4 in extracellular spaces with different intensity of staining (11 weak, 12 strong), whereas only 13 of GERD children stain positively for IgG4 (10 weak, 3 strong). 11 GERD children versus only 1 EoE child showed negative staining for IgG4 in extracellular spaces (p value 0.002). Among those stain positively for IgG4, the distribution of IgG4 reaction (in extracellular spaces) was focal in 13 EoE cases and 13 GERD children whereas diffuse reaction was found in 10 EoE cases and none of GERD children (p value≤0.001). These results are shown in table 3 and figure 2.

Table (3): IgG4 among the study and control groups

	Study group (no=24)	Control group (no=24)	p value
IgG4 in plasma cells/HPF Median (Min-Max)	5.0 (0-30)	0.0 (0-8)	**≤0.001***
IgG4 in extracellular spaces **Negative** **Weak** **Strong**	 1 (4.2%) 11 (45.8%) 12 (50%)	 11 (45.8%) 10 (41.6%) 3 (12.6%)	**0.002***
IgG4 number in epithelial cells Median (Min-Max)	2.0 (0-3)	1.0 (0-3)	**≤0.001***
Distribution of IgG4 **No IgG4 present** **Focal** **Diffuse**	 1 (4.2%) 13 (54.2%) 10 (41.6%)	 11 (45.8%) 13 (54.2%) 0 (0.0%)	**≤0.001***

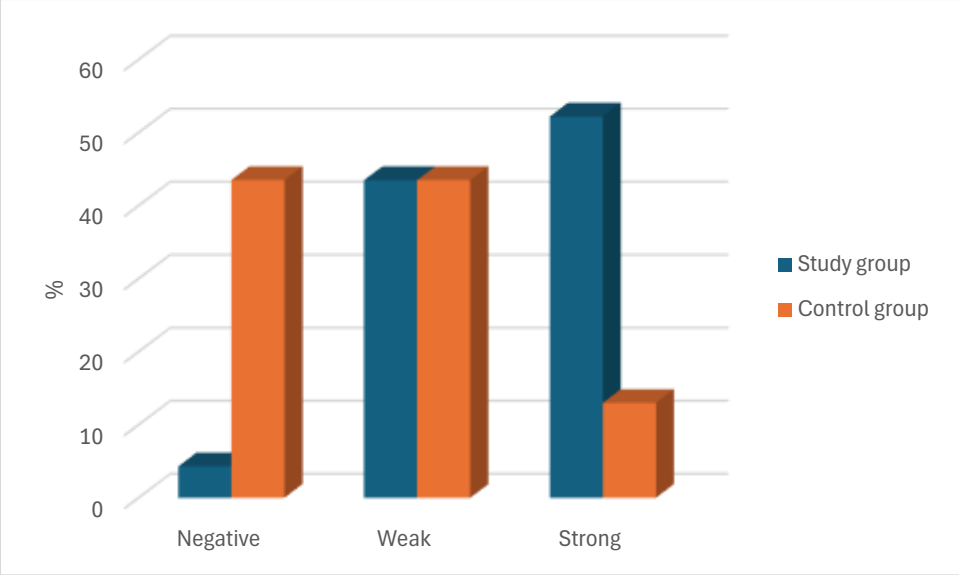

Figure (2): IgG4 in extracellular spaces among the study and control groups

Discussion:

Current study is a record of oesophageal IgG4 staining in pediatric children with newly diagnosed, treatment naïve eosinophilic esophagitis. This study supports the newly identified relation between EoE and IgG4 staining and complements this with clinical characteristics of the patients.

Among EoE cases in our study, 22 were males and only 2 were females, this agrees with findings in the literature that males are more commonly affected by EoE. Clinical presentations varied between EoE cases and controls (children with GERD). EoE cases presented mainly by dysphagia (10 cases) while only 1 GERD patient presented mainly by dysphagia (p value 0.004). The main clinical presentation among GERD children was nausea and vomiting (16 out of 24) versus 6 EoE cases (p value 0.003). Other clinical features also varied between cases and controls. For example, food impaction was more common among EoE cases (5 cases versus non of the controls, p value 0.018). Although no statistically significant differences, food aversion, chocking, gaging and early satiety were more common among EoE cases in comparison to controls whereas upper GI bleeding was more common among GERD patients. Abdominal pain, heart burn and chest pain were found similarly between cases and controls.

Endoscopy:

Endoscopic examination is an essential component in EoE diagnosis, as it allows direct visualization of characteristic esophageal changes and collection of biopsy samples for histopathological analysis (Aceves et al., 2022). Six biopsies or more have to be acquired, with special care to visible lesions and biopsies taken from the proximal, mid, and distal segments of the oesophagus. In paediatrics with EoE, biopsies have to be haphazardly taken from the proximal and distal oesophagus, regardless of endoscopic mucosal appearance, as normal mucosa is frequently detected (Oliva et al., 2025). Common endoscopic results in EoE include mucosal oedema, oesophageal rings or “trachealization”, white exudates or plaques, linear furrows and strictures as major features, crepe paper oesophagus and oesophageal tears as minor features (Hirano et al., 2013).

In our study, EoE cases showed variable gross endoscopic features. The most common features were linear furrows (79.2%) and edema (62.5%), followed by exudate (41.6%) and rings (37.5%). Children with GERD showed none of these features. Esophageal stricture was found in four EoE patient versus two GERD patient. On the other side, grossly free endoscopy was found in seven GERD patients versus only one EoE case (p value 0.047)

IgG4:

The role IgG4 in EoE is being increasingly investigated in multiple studies, both pediatrics and adult studies.
Our study revealed statistically significant differences between cases and controls regarding immunohistochemical analysis of IgG4 in esophageal biopsies. IgG4 presented in higher numbers in plasma cells of eosinophilic esophagitis cases compared to children with GERD (p value≤0.001). Also, IgG4 number in esophageal epithelial cells was significantly higher in EoE cases versus children with GERD (p ≤0.001).

Furthermore, there were significant differences regarding IgG4 reaction in extracellular spaces. 23 EoE cases stained positively for IgG4 in extracellular spaces with different intensities of staining (11 weak, 12 strong) whereas only 13 of children with GERD stained positively for IgG4 (10 weak, 3 strong reaction). 11 GERD children versus only 1 EoE child showed negative staining for IgG4 in extracellular spaces (p 0.002). Among those stained positively for IgG4, the distribution of IgG4 reaction (in extracellular spaces) was focal in 13 EoE cases and 13 GERD children whereas diffuse reaction was found in 10 EoE cases and none of GERD children (p value≤0.001).

Similar to our results, Clayton et al. (2014) evaluated the role of IgG4 in EoE and revealed an increase in the level of IgG4 positive plasma cells in the lamina propria and granular extracellular IgG4 deposits without an increase of the remaining IgG subclasses, immunoglobulin M or immunoglobulin A values. They stated that cases with EoE had a 45-fold increase in oesophageal IgG4 compared with controls. IgG4 may also help to differentiate EoE from GERD according to different studies. Wong et al. (2020) collected oesophageal biopsies from cases with confirmed EoE and GERD and IHC for IgG4 was performed. They concluded that IgG4 can be a useful marker to distinguish EoE from GERD. In addition, Zukerberg et al. in their study noticed that intrasquamous deposits of IgG4 can discriminate between patients with GERD and those with EOE (Zukerberg et al., 2016). In another study, the authors recognized intercellular and extracellular IgG4-Dep in cases with EoE, IgG4 positive plasma cells (IgG4-PC) were primarily situated in the subepithelial stroma of the lamina propria and their content was 145 times greater compared to cases with GERD. Remarkably, a drop in IgG4-PC levels was noticed following eight weeks of treatment with the topical budesonide with clinical improvement (Weidlich et al., 2020).

Also, several pediatric studies evaluated the role of IgG4 in children with EoE. A research of 41 paediatric cases with EoE demonstrated elevated levels of IgG4-positive plasma cells in correlation with active oesophagitis, especially in cases with food allergy (Mohammad et al., 2018). Another study of 17 paediatric cases with EoE revealed that oesophageal IgG4 levels were increased in affected cases and correlated with disease activity as evaluated by histopathology and transcriptomic characteristics (Rosenberg et al., 2018). In a research conducted by pope et al., 2019, they compared oesophageal IgG4 quantification in 31 treatment naïve, newly diagnosed EoE cases (16 paediatrics, 15 adults) to 4 paediatric reflux patients and 4 paediatric controls. Compared to children with reflux esophagitis or controls, they found that EOE cases had a considerably higher likelihood of positively staining for IgG4, with 48% of EoE cases doing so and none of the reflux esophagitis or control cases. They concluded that IgG4 staining had 48% sensitivity and 100% specificity for EoE. In another study to define the prevalence of immunoglobulin G (IgG) and its subclass IgG4 in IHC in oesophageal biopsies of children with EOE (active EOE and EOE in remission) in comparison to children with GERD, the study revealed that initial oesophageal biopsies from pediatric patients with active EOE showed a significant increase in IgG-positivc staining compared with those in children with EOE in remission or with GERD (Rizvi et al., 2022). In a recent pediatric study to identify the role of IgG4 in EoE in 32 pediatric patients. IgG4-positive plasma cells were present in 76.5% of cases. Patients received variable treatments, with many receiving proton pump inhibitors and topical steroids, but dupilumab individuals showed notable improvement. This emphasizes the need for standardized practices and detailed assessments and that IgG4 may have a possible role in EoE pathophysiology (Gonzalez-Uribe et al., 2024).

Collectively, this study implicates the important role of IgG4 in EoE.

Conclusion:

our study implicates the potential role of IgG4 in esophageal biopsies in children with EoE at diagnosis. Further pediatric studies are needed to confirm this finding which may help to tailor EoE therapies in the future.

Conflict of interest: None.

Fund: None.

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