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The Association between Celiac Disease and Eosinophilic Esophagitis among Children, in Isfahan, Iran

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Abstract

Background: The prevalence of eosinophilic esophagitis (EoE) has increased in recent decades. Recent studies have found that the prevalence of EoE in patients with celiac disease (CD) is much higher compared with the general population. In this study, the prevalence of EoE in children with CD was calculated and their clinical symptoms, endoscopic and histopathological findings were compared.

Methods: This was a retrospective study conducted on the data records of the patients diagnosed with celiac disease during 2012-2020, and registered at Imam Hossein Children's Hospital and the Institute of the Celiac Association in Isfahan, Iran. Clinical findings, endoscopic reports, serological and histopathological data of the patients were recorded and analyzed.

Results: A total of 80 children with CD were included in the study. The mean age of the patients with CD and EoE (n=8) was 7.75± 3.99 years, and in children with CD alone (n=72), the mean age was 7.85± 3.83. The most common clinical findings were abdominal pain, anorexia, diarrhea and constipation. There were no significant differences in the symptoms of either group. The most common endoscopic view was duodenal scalloping and esophagitis; and 50% of EoE patients had a normal endoscopic view of the esophagus. With regards to serological findings, the level of TTG-IgA (U/ml) in the CD and EoE group was higher than the CD group (183.73 ± 101.54 vs. 117.07 ± 95.34 U/ml); however, no statistically significant difference was observed.

Conclusion: Our study found that the prevalence of EoE in children with CD appears to be higher than in previous studies. We have also shown that the presence of EoE cannot be detected solely based on clinical and even endoscopic results. Therefore, an esophageal biopsy is recommended in celiac patients.

Key Words: Celiac disease, children, Eosinophilic esophagitis, Epidemiology, Upper gastrointestinal tract.

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1- INTRODUCTION

Eosinophilic esophagitis (EoE) and celiac disease (CD) are two different immunological diseases of the upper gastrointestinal tract, with distinct histological and clinical manifestations (1). EoE is a chronic immune-mediated esophageal disease, which is clinically characterized by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation (2).

The incidence of EoE seems to be increasing over the past decades, from 0.35 per 100,000 persons to 9.45 per 100,000 (3) and the prevalence of EoE is estimated to be around 1 in 1,000 persons (4). The diagnosis of EoE is based on clinical symptoms, endoscopic findings and biopsy; the presence of ≥15 eosinophils per high power field is needed for diagnosis. It is also necessary to exclude other causes which may be responsible for the symptoms and signs observed (5). The symptoms of EoE in children can vary according to their age, the most common being feeding dysfunction, vomiting, abdominal pain, food impaction, and dysphagia (6). The association of EoE with other allergic conditions has been demonstrated in various studies. EoE is strongly associated with food allergies, environmental allergies, asthma and dermatitis (7-9). The association of EoE with chronic rhinosinusitis and inflammatory bowel disease has also been investigated (10, 11). In addition, it should be noted that its association with celiac disease has also been investigated in multiple studies, but the evidence supporting this association is insufficient (12, 13). In EoE, the mechanisms of the host immune system appear to be stimulated by immunoglobulin E (IgE) as well as delayed T helper type 2 (Th2) cells. Little is known about the role of chemokines, cytokines, and microRNAs in the pathophysiology of EoE (14, 15).

CD, also known as gluten-sensitive enteropathy, is a common chronic inflammatory disease of the small intestine. The approximate prevalence of CD in the general population is 0.5 to 1%, varying among different countries (16). However, it has been suggested that the prevalence of CD is underestimated in developing countries (17). Besides the environmental factors (gluten), genetic factors have important roles in the development of CD with approximately 99% of people with CD having human leukocyte antigen (HLA) DR3-DQ2 and/or DR4-DQ8, compared to approximately 40% of the general population (18). CD usually occurs in children up to 2 years old. The symptoms commonly experienced are diarrhea, abdominal pain, anorexia and failure to thrive (19).

Diagnosis of CD is made by clinical evaluation, serological tests (e.g. IgA antibodies against tissue transglutaminase "TTG-IgA") and biopsy (20). CD is strongly associated with type 1 diabetes, selective IgA deficiency and autoimmune thyroiditis (21, 22).

Some studies have examined the relationship between EoE and CD (12, 13); however, more evaluations are still needed, so due to the limited data available in our country, in this study, we decided to evaluate the relationship between these two diseases as well as their differences in clinical and histopathological features.

2- METHODS

2-1. Study design and population

This retrospective study is conducted on the data records of the patients diagnosed with celiac disease during 2012-2020, and registered at the Imam Hossein Children's Hospital and the Institute of the Celiac Association in Isfahan, Iran. The study participants were children aged 2 to 18 years who had been diagnosed with Celiac Disease (CD). A total of 80 participants were included in the study, the

information of whom was kept confidential. The research protocol has been approved by the Research Center of the Isfahan University of Medical Sciences and the Human Investigation Ethics Committee.

2-2. Study procedure

We used the hospital records of the patients diagnosed with CD, who had referred to Imam Hossein Children's Hospital and the Iranian Institute of the Celiac Association, during 2012- 2020. CD was diagnosed by a gastroenterologist based on clinical assessment, intestinal biopsy, and serologic tests (TTG-IgA >10). To diagnose eosinophilic esophagitis (EoE), esophageal biopsies were performed at the same time. Four biopsies were taken from the distal portion of the esophagus and 2 biopsies were taken from the middle part. Gastric and duodenal biopsies were also taken simultaneously to rule out eosinophilic gastroenteritis. Diagnosis of EoE was based on the presence of more than 15 eosinophils per high power field (HPF), endoscopic findings compatible with EoE such as furrowing, trachealization, whitish exudate, esophageal rings, diffuse narrowing, fragile mucosa, clinical symptoms and ruling out of other causes. All histopathological specimens were examined by an expert pathologist. Eosinophil levels in peripheral blood were also assessed. Eosinophil counts > 450/μL was considered as eosinophilia; and hypereosinophilia was defined as an elevation in the number of eosinophils above 1500/μL.

2-3. Data analysis

All tests were computed with a 95% confidence interval (CI) and all statistical analyses were performed with SPSS Version 25.0. All data are presented as mean ± standard deviation (SD). To assess normal distribution the Kolmogorov-Smirnov test was performed and Mann-Whitney test was used to compare the clinical and histopathological features of the diseases.

3- RESULTS

In this study, 80 children and adolescents with CD during 2012-2020 were included. In children with CD, 10% (n=8) also met the EoE diagnostic criteria. The mean age of the patients with CD and EoE was 7.75± 3.99 years and the gender ratio was 1:1. Clinical, endoscopic, histopathological and serological findings of the patients with CD and EoE are shown in **Table 1**. The most common clinical symptoms were abdominal pain (n=3; 37%) and anorexia (n=3; 37%) and the most common history of allergies was food allergy (n=2; 25%). Duodenal scalloping was also the most common endoscopic finding in patients with CD and EoE (n=7; 87.5%).

For children with CD without EoE (n=72), the mean age was 7.85±3.83 years and the gender ratio was almost the same (males=35 and females=37). The most common clinical symptoms were abdominal pain (n=39; 54.2%), constipation (n=23; 31.9%) and anorexia (n=22; 30.6%). Furthermore, the most common allergic history was food allergy (n=7; 9.7%) followed by allergic rhinitis (n=5; 6.9%). In addition, in the endoscopic evaluation, the most common findings were duodenal scalloping (n=54; 75%), esophagitis (n=37; 51.4%), intestinal atrophy (n=23; 31.9%) and intestinal fissuring (n=17; 23.6%). All patients' information, including clinical symptoms, endoscopic results, and serological tests are presented in **Table 2**.

Regarding the serological findings, the level of TTG-IgA (U/mL) in the CD and EoE group was higher than that in the CD group (183.73 ± 101.54 vs. 117.07 ± 95.34 U/mL); however, the difference did not reach the statistical significance (P= 0.63).

This was also the case for the number of peripheral blood eosinophils; the eosinophil counts in the CD and EoE group were 170.50 ± 79.59, and for CD alone was 147.31 ± 113.565; but no statistically significant difference was observed (P= 0.24). **Table 2** shows the comparisons between the two groups for all variables.

4- DISCUSSION

Celiac disease (CD) and eosinophilic esophagitis (EoE) are two clinically and histopathologically distinct diseases that involve the upper gastrointestinal tract. From an immunological point of view, EoE appears to be associated with T helper type 2 (Th2) cells and immunoglobulin E (IgE), while CD is associated with Th1 cells and gluten intake (23).

The incidence and prevalence of eosinophilic esophagitis has been increasing at rates higher than those previously estimated. In addition, recent studies have shown a higher prevalence of EoE in CD patients than in the general population (12). In a study on 221 patients with CD between 1999 to 2007, Ooi et al. found that the prevalence of EoE was 3.2 percent which is higher than that in the general population; They also suggested that an esophageal biopsy may be useful in the assessment of patients with CD (24).

Table-1: The characteristics, clinical, Endoscopic, and histopathological features of children with CD and EoE

Patient no.	Gender/Age (year)	Symptoms	Endoscopy	Allergy history	intraepithelial esophageal count	Blood Eosinophil count	TTG-IgA level
1	Female/9	Abdominal Pain/ Constipation/ Nausea/ Bloating/Anorexia/ Alopecia	Esophageal erythema and edema/ Esophagitis/ Duodenal scalloping and atrophy	none	25	82	296
2	Female/4	Diarrhea/ Jaundice	Duodenal scalloping and atrophy	none	20	195	200
3	Male/5	Failure to thrive	Esophageal Mucosal Furrows/ Esophagitis/ Duodenal scalloping/ Duodenitis	none	40	80	100.5
4	Female/ 10	Failure to thrive/ Constipation/ Bloating/ Anorexia	Duodenal scalloping	none	20	319	348
5	Male/4	Nausea/ Steatorrhea/ Anemia/ Anorexia	Esophageal erythema and edema/ Esophagitis	Urticaria / Food Allergy	20	160	57.4
6	Male/7	Dysphagia	Duodenal scalloping/ Duodenitis	none	20	212	88
7	Female/ 16	Abdominal Pain	Esophagitis/ Duodenal scalloping	Asthma/ food allergy	20	200	180
8	Male/ 7	Abdominal Pain/ Diarrhea/ weight loss/	Duodenal scalloping/ Intestinal fissuring	none	20	116	200

Table-2: Comparison between CD alone and CD in association with Eosinophilic esophagitis (EoE)

Variable		CD (n = 72) Mean ± SD or n (%)	CD and EoE (n = 8) Mean ± SD or n (%)	P-Value
Demographics				
Gender	Male/Female	35 (48.6)/37 (51.4)	4 (50)/4 (50)	0.94
	Age (Year)	7.85 ± 3.83	7.75 ± 3.99	0.87
Duration of Symptoms (month)		23.10 ± 27.54	19.5 ± 16.92	0.81
Symptoms	Abdominal Pain	39 (54.2)	3 (37.5)	0.37
	Dysphagia	8 (11.1)	1 (12.5)	0.90
	failure to thrive	17 (23.6)	2 (25)	0.93
	Diarrhea	12 (16.7)	2 (25)	0.55
	Constipation	23 (31.9)	2 (25)	0.69
	Nausea	16 (22.2)	2 (25)	0.85
	Weight loss	10 (13.9)	1 (12.5)	0.91
	Steatorrhea	11 (15.3)	1 (12.5)	0.83
	Bloating	18 (25)	2 (25)	1.00
	Jaundice	10 (13.9)	1 (12.5)	0.91
	Anorexia	22 (30.6)	3 (37.5)	0.69
	Bone Pain	8 (11.1)	1 (12.5)	0.32
	Alopecia	10 (13.9)	1 (12.5)	0.91
	Arthralgia	12 (16.7)	0 (0)	0.21
	Anemia	16 (22.2)	1 (12.5)	0.52
History of Allergies	Asthma	2 (2.8)	1 (12.5)	0.17
	Allergic Rhinitis	5 (6.9)	0 (0)	0.44
	Urticaria	4 (5.6)	1 (12.5)	0.44
	Food Allergy	7 (9.7)	2 (25)	0.19
Endoscopic features	Normal Esophagus	26 (36.1)	4 (50)	0.44
	Ringed Esophagus	0 (0)	0 (0)	1.00
	Esophageal Mucosal Furrows	2 (2.8)	1 (12.5)	0.17
	Esophageal White Plaque	2 (2.8)	0 (0)	0.63
	Erythema	8 (11.1)	2 (25)	0.26
	Erosion	2 (2.8)	0 (0)	0.63
	Edema	1 (1.4)	2 (25)	0.001
	Mucosal Break	1 (1.4)	0 (0)	0.73
	Nodularity	1 (1.4)	0 (0)	0.73
	Esophagitis	37 (51.4)	4 (50)	0.94
	Normal Duodenum	7 (9.7)	1 (12.5)	0.80
	Scalloping	54 (75)	7 (87.5)	0.43
	Intestinal fissuring	17 (23.6)	1 (12.5)	0.47
	Atrophy	23 (31.9)	2 (25)	0.69
	Intestinal Erythema	7 (9.7)	0 (0)	0.35
	Duodenitis	8 (11.1)	2 (25)	0.26
	Duodenal Edema	2 (2.8)	0 (0)	0.63
	Mosaic Pattern	2 (2.8)	0 (0)	0.63
Histopathological features	TTG-IgA (U/mL)	117.07 ± 95.34	183.73 ± 101.54	0.63
	Peripheral Blood Eosinophils	147.31 ± 113.565	170.50 ± 79.59	0.24
	Esophageal Eosinophil	0.00	23.13 ± 7.04	0.000

Leslie et al., similarly, using esophageal biopsies, evaluated 121 children with CD, reporting that the prevalence of EoE in children with CD is at least 4%. They also showed that 30% of the patients with EoE and CD had a normal endoscopic view, whereas the biopsy findings showed evidence of EoE (25). In the present study, the prevalence of EoE among children with CD was estimated at 10%. This rate is almost similar to the study of Dharmaraj et al., Who studied 56 patients with CD and reported the prevalence of EoE to be 10.7% (12).

In line with the previous research, the present study demonstrates that the prevalence of EoE in patients with CD is much higher than in the general population, which can indicate a link between the two diseases. The response to a gluten-free diet in EoE patients has been reported differently in previous studies. Some studies have shown that a gluten-free diet can improve the symptoms and pathological outcomes of EoE. However, other studies have shown that this diet has no effect on EoE improvement (12, 13, 26).

In our study, the clinical, endoscopic and histopathological findings of the patients with EoE and CD were compared with those of the patients with CD alone. Our results show that the two diseases cannot be differentiated only by clinical signs and even endoscopic results. It should be emphasized again that 50% of the patients with EoE had a normal endoscopic view of the esophagus. Therefore, it is recommended that the patients with CD undergo an esophageal biopsy to rule out EoE. It also appears that the level of TTG-IgA in serological testing of the patients with EoE and CD is higher than that in the patient with CD alone, although more measurements with higher sample sizes are required to confirm this observation. Furthermore, due to the high prevalence of EoE in patients with CD, the use of proton pump inhibitors (PPIs) and topical glucocorticoids may be helpful in symptom management (26, 27).

5- CONCLUSION

The prevalence of EoE in children with CD, estimated as 10% in our study, seems to be higher than that reported by previous studies. This study also revealed that the presence of EoE could not be detected only based on clinical and even endoscopic findings, so an esophageal biopsy is recommended for the patients with CD. In addition, due to the higher level of TTG-IgA in EoE patients, we recommend further research to evaluate the potential use of this test as a screening tool for EOE patients.

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