Pediatr Gastroenterol Hepatol Nutr. 2024 Mar;27(2):79-87
https://doi.org/10.5223/pghn.2024.27.2.79
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Original Article

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Serum Eosinophilic Cationic Protein as a Useful Noninvasive Marker of Eosinophilic Gastrointestinal Disease in Children

Hae Ryung Kim,[1] **Youie Kim**,[2] **Jin Soo Moon**,[3] **Jae Sung Ko**,[3] **and Hye Ran Yang**[1,3]

[1]Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Korea
[2]Department of Pediatrics, Incheon St. Mary's Hospital, Incheon, Korea
[3]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea

OPEN ACCESS

Received: May 25, 2023
Revised: Sep 22, 2023
Accepted: Sep 23, 2023
Published online: Mar 4, 2024

Correspondence to
Hye Ran Yang
Department of Pediatrics, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Email: hryang@snubh.org

ORCID iDs
Hae Ryung Kim
https://orcid.org/0009-0005-4083-2877
Youie Kim
https://orcid.org/0000-0002-6839-9244
Jin Soo Moon
https://orcid.org/0000-0001-9760-297X
Jae Sung Ko
https://orcid.org/0000-0002-3064-2974
Hye Ran Yang
https://orcid.org/0000-0002-3423-6922

Funding
None.

ABSTRACT

Purpose: Recently, the prevalence of eosinophilic gastrointestinal disease (EGID) has shown an increasing trend worldwide. As the diagnosis of EGID requires invasive endoscopy with biopsy, noninvasive markers for detecting EGID in suspected patients, particularly children, are urgently needed. Therefore, this study aimed to evaluate the diagnostic accuracy of serum eosinophil cationic protein (ECP) beyond peripheral eosinophil counts in pediatric patients with EGID.
Methods: Overall, 156 children diagnosed with EGID were enrolled and 150 children with functional abdominal pain disorder (FAPD) were recruited as controls. All participants underwent endoscopic biopsy in each segment of the gastrointestinal (GI) tract and serum ECP measurement, as well as peripheral eosinophil percent and absolute eosinophil count.
Results: Comparing EGID (n=156) with FAPD (n=150) patients, serum ECP levels were significantly higher in pediatric patients with EGID than in those with FAPD (25.8±28.6 μg/L vs. 19.5±21.0 μg/L, p=0.007), while there was no significant difference in peripheral eosinophil percent and absolute eosinophil counts between the two groups. Serum ECP levels were correlated with peripheral eosinophil percent (r=0.593, p<0.001) and the absolute eosinophil count (r=0.660, p<0.001). The optimal cutoff value of serum ECP for pediatric EGID was 10.5 μg/mL, with a sensitivity of 69.9% and a specificity of 43.4% with an area under the receiver operating characteristic curve of 0.562.
Conclusion: The combination of serum ECP levels and peripheral eosinophil counts, when employed with appropriated thresholds, could serve as a valuable noninvasive biomarker to distinguish between EGID and FAPD in pediatric patients manifesting GI symptoms.

Keywords: Eosinophilic esophagitis; Eosinophil cationic protein; Eosinophil; Diagnosis; Child

INTRODUCTION

Eosinophilic gastrointestinal disease (EGID) is a mixed form of immune-mediated food allergy that selectively affects the different segments of the gastrointestinal (GI) tract. EGID can be further classified based on the location of eosinophilic infiltration, as follows: eosinophilic esophagitis (EoE), eosinophilic gastritis (EoG), eosinophilic enteritis (EoN),

Conflict of Interest
The authors have no financial conflicts of interest.

and eosinophilic colitis (EoC) [1]. Although EGID is rare, in recent years, the global diagnosis of EGID has shown an increase, possibly owing to increasing interest and better recognition of the disease [2,3]. In United States, the prevalence of EGID was reported to be 17.9-30 per 100,000 adults and 19.4 per 100,000 children [4,5].

EGID is characterized by tissue eosinophilia of the GI tract and various GI symptoms, including abdominal pain, vomiting, and diarrhea [6]. As these symptoms are common and nonspecific in children, the diagnosis of EGID generally requires the presence of the following; recurrent or persistent GI symptoms, pathologically increased tissue eosinophils per high power field (HPF) of the related GI biopsy specimens, and the absence of secondary causes of GI tissue eosinophilia [7,8]. Failure to perform invasive endoscopy with biopsy based on the above diagnostic criteria can result in underdiagnosis of EGID, especially in pediatric patients.

Regarding noninvasive screening of EGID, an increase in peripheral eosinophil counts has been used with some limitations [9]. Furthermore, in our previous study published in 2020, fecal calprotectin level was introduced as a useful and reliable noninvasive marker to differentiate EGID from functional abdominal pain disorder (FAPD) in children when an optimal cutoff limit was applied [10]. However, since calprotectin is an intracellular protein found in the cytosol of neutrophils and is correlated with leukocyte excretion in the feces of the patients with intestinal inflammation, its generalizability as a marker for diagnosing EGID is limited.

Eosinophilic cationic protein (ECP) is a cytotoxic granule protein released from eosinophils that degranulates on stimulation, releasing toxic mediators causing tissue damage and inflammation. Serum ECP has so far been mainly studied as a noninvasive marker of some allergic diseases, such as asthma, allergic rhinitis, and atopic dermatitis. Recent studies on serum ECP in EoE have reported significantly higher serum ECP levels in patients with EoE [11]. However, to the best of our knowledge, there have been no studies investigating the clinical significance of measuring serum ECP levels as a noninvasive screening tool in children with EGID other than EoE. Therefore, this study aimed to evaluate the diagnostic accuracy of serum ECP beyond peripheral eosinophil count in pediatric patients with EGID.

MATERIALS AND METHODS

Participants

This was a single center, retrospective cohort study conducted on pediatric patients EGID and FAPD between April 2015 and July 2021. Children and adolescents aged ≤18 years diagnosed with either EGID or FAPD were considered eligible.

EGID was diagnosed according to the diagnostic criteria for EGID suggested by Talley et al. [8] in 1990, which uses the following clinical, laboratory, radiologic, endoscopic, and histopathologic findings: 1) presence of GI symptoms; 2) histological demonstration of eosinophilic infiltration into the GI tract; and 3) exclusion of other causes of tissues eosinophilia [8]. The histopathologic diagnosis of EGID was made when the total number of infiltrating eosinophils per HPF exceeded 15 in the esophagus (EoE), 30 in the stomach (EoG), 20 in the duodenum and small intestine (EoN), 50 in the right-sided colon, 35 in the transverse colon, and 25 in the left-sided colon (EoC) [4,12].

Children who met the ROME IV criteria without any evidence of organic diseases in the above-mentioned evaluation were included in the FAPD group as a control [13]. The FAPD group included patients with various disease subtypes, including functional dyspepsia, irritable bowel syndrome, and childhood functional abdominal pain. Children with a significant allergic diseases such as allergic rhinitis, atopic dermatitis, allergic conjunctivitis, asthma, and IgE-mediated food allergy were excluded from the study.

Endoscopic- and histopathological evaluation

All children underwent both esophagogastroduodenoscopy and colonoscopy with biopsies following presentation with chronic or recurrent GI symptoms. Esophagogastroduodenoscopy was performed using a GIF-Q260 or GIF-XP260 (Olympus), and colonoscopy was performed using a PCF-Q260AL, GIF-Q260, or GIF-XP260 scope (Olympus).

Tissue samples were collected by endoscopic biopsy from each segment of the GI tract, including the esophagus, gastric antrum, gastric body, duodenum, terminal ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. These biopsy specimens were immediately formalin fixed and processed by embedding in paraffin wax. Thin cross sections measuring 3 μm in thickness were cut from the paraffin block and stained with hematoxylin-eosin. The eosinophil count was determined by examining five randomly selected high-power fields, with quantification of eosinophils performed at ×400 magnification using an Axioskope40 microscope (Mirax-Carl Zeiss) [14].

Laboratory investigation

All children underwent laboratory tests including white blood cell count (WBC), absolute neutrophil count (ANC), peripheral eosinophil percent (%) and absolute eosinophil counts, erythrocyte sedimentation rate (ESR), and highly sensitive C-reactive protein (hsCRP). An absolute eosinophil count of >500 μL was defined as peripheral eosinophilia.

Measurement of serum ECP

Serum ECP levels were assessed in all participants following diagnosis. These assessments were conducted using the Phadia ImmunoCAP system ECP FEIA (Phadia AB), in accordance with the manufacturer's instruction. The normal range of serum ECP in the laboratory-established patient population was 2.0–18.0 μg/L [15].

Statistical analysis

The baseline characteristics of the patients were summarized using descriptive statistics. The data were described as the number (%) for categorical variables and mean and standard deviation for continuous variables.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Co.) statistical software. The Chi-square test was applied to analyze categorical variables. Student's *t*-test was performed to analyze continuous variables. Bivariate correlation analyses were performed using the Pearson correlation for parametric tests. A p-value <0.05 was considered significant. Finally, receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of serum ECP.

Ethics

This study was approved by the Institutional Review Board of Seoul University Bundang Hospital (IRB approval number: B-2212-798-102 20221104). This study was not subject to the

Medical Research Involving Human Subjects Act, as it involved only the collection of data generated by routine medical care. All data were collected and recorded by the investigators in such a manner that participants could not be identified.

RESULTS

Patient characteristics

A total of 306 children (166 males, 140 females; mean age of 11.0±4.8 years) were recruited and stratified into the EGID group (n=156) and the FAPD control group (n=150). Baseline demographic and laboratory findings are listed and compared between the two groups in **Table 1**. There were no significant differences in either peripheral eosinophil percent or absolute eosinophil counts between the EGID and FAPD groups (**Table 1**).

Comparison of serum eosinophil cationic protein level

Serum ECP levels were significantly higher in pediatric patients with EGID than in those with FAPD (25.8±28.6 μg/L in EGID vs. 19.5±21.0 μg/L in FAPD, p=0.007) (**Table 1**, **Fig. 1**). WBC count (7,160.9±2,652.2 μL vs. 6,816.7±1,697.3 μL, p=0.004), ESR (8.8±9.6 mm/hr vs. 6.3±5.2

Table 1. Comparison of laboratory findings between children with EGID and those with FAPD

Variable	FAPD (n=150)	EGID (n=156)	p-value
Male	84 (56.0)	82 (52.6)	0.541
Age (yr)	11.1±3.8	11.0±5.6	0.867
WBC (mL)	6,816.7±1,697.3	7,160.9±2,652.2	0.004*
ANC (mL)	3,377.5±1,363.9	3,387.6±1,643.7	0.123
ESR (mm/hr)	6.3±5.2	8.8±9.6	<0.001*
hsCRP (mg/dL)	0.1±0.2	0.2±0.5	0.002*
Peripheral eosinophil percent (%)	2.9±2.5	3.5±3.3	0.295
Absolute eosinophil count (mL)	192.3±170.6	236.2±216.2	0.245
Serum ECP (mg/L)	19.5±21.0	25.8±28.6	0.007*

Values are presented as number (%) or mean±standard deviation.
EGID: eosinophilic gastrointestinal disease, FAPD: functional abdominal pain disorder, WBC: white cell count, ANC: absolute neutrophil count, ESR: erythrocyte sedimentation rate, hsCRP: highly sensitive C-reactive protein, ECP: eosinophil cationic protein.
*p-value<0.05 indicates statistical significance.

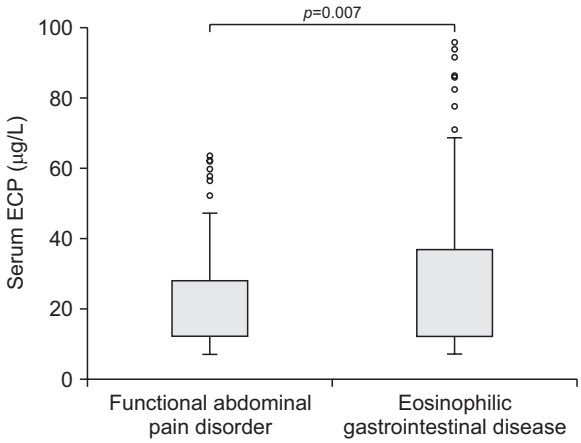

Fig. 1. Comparison of the mean serum eosinophil cationic protein levels in pediatric patients with eosinophilic gastrointestinal disease and those with functional abdominal pain disorder.
ECP: eosinophil cationic protein.

https://doi.org/10.5223/pghn.2024.27.2.79

mm/hr, $p<0.001$), and hsCRP (0.2±0.5 mg/dL vs. 0.1±0.2 mg/dL, $p=0.002$) were also higher in patients with EGID than in those with FAPD. There were no differences between the two groups in terms of the peripheral eosinophil percent and absolute eosinophil count.

Correlation between serum eosinophil cationic protein with absolute eosinophil counts and inflammatory parameters

Regarding laboratory parameters, WBC, peripheral eosinophil percent, absolute eosinophil count, and ESR were all correlated with serum ECP (**Table 2**). In particular, serum ECP revealed significant correlation with both peripheral eosinophil percent (r=0.593, $p<0.001$) and absolute eosinophil count (r=0.660, $p<0.001$) (**Table 2**).

Diagnostic accuracy of serum eosinophil cationic proteins in children with eosinophilic gastrointestinal diseases

In the ROC analysis of serum ECP level between the pediatric EGID and FAPD control groups, the areas under the ROC curve (AUROC) for serum ECP was 0.562 (95% confidence interval 0.495–0.629). According to the ROC analysis, the optimal cutoff value of serum ECP for pediatric EGID was 10.5 μg/mL with a sensitivity of 69.9%, a specificity of 43.4%, a positive predictive value of 62.8%, and a negative predictive value of 38.1% (**Fig. 2**).

Table 2. Correlation between serum eosinophil cationic protein level and other laboratory parameters

Variable	WBC	ANC	ESR	hsCRP	Peripheral eosinophil percent	Absolute eosinophil count	ECP
WBC (mL)							
r	1.000	0.735	0.317	0.108	−0.103	0.155	0.184
p-value	-	<0.001*	<0.001*	0.065	0.072	0.007*	0.002*
ANC (mL)							
r	0.735	1.000	0.359*	0.221	−0.206	−0.024	0.068
p-value	<0.001*	-	<0.001*	<0.001*	<0.001	0.676	0.254
ESR (mm/hr)							
r	0.317	0.359	1.000	0.512	−0.076	0.008	0.129*
p-value	<0.001*	<0.001*	-	0.000*	0.206	0.890	0.038
hsCRP (mg/dL)							
r	0.108	0.221	0.512	1.000	−0.046	−0.009	0.106
p-value	0.065	<0.001*	<0.001*	-	0.434	0.872	0.080
Peripheral eosinophil percent (%)							
r	−0.103	−0.206	−0.076	−0.046	1.000	0.941	0.594
p-value	0.072	<0.001*	0.206	0.434	-	<0.001*	<0.001*
Absolute eosinophil count (mL)							
r	0.155	−0.024	0.008	−0.009	0.941*	1.000	0.660
p-value	0.007	0.676	0.890	0.872	<0.001	-	<0.001*
Serum ECP (mg/L)							
r	0.184	0.068	0.129	0.106	0.594	0.660	1.000
p-value	0.002*	0.254	0.038*	0.080	<0.001*	<0.001*	-

WBC: white cell count, ANC: absolute neutrophil count, ESR: erythrocyte sedimentation rate, hsCRP: highly sensitive C-reactive protein, ECP: eosinophil cationic protein, −: not available.
*p-value<0.05 indicates statistical significance.

https://doi.org/10.5223/pghn.2024.27.2.79

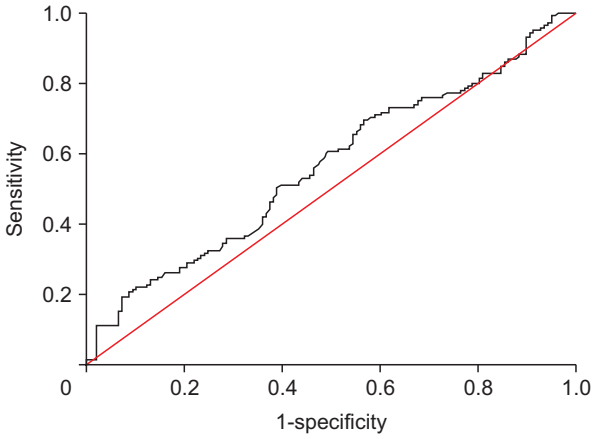

Fig. 2. Receiver operating characteristic curve of serum eosinophil cationic protein levels with an optimal cutoff of 10.5 μg/mL for differentiating eosinophilic gastrointestinal disease from functional abdominal pain disorder.

DISCUSSION

To the best of our knowledge, this is the first study to investigate clinical significance and diagnostic accuracy of serum ECP measurement as a noninvasive screening tool in children with EGID other than EoE. Our study results revealed that serum ECP levels significantly increased in pediatric patients with EGID compared to those with FAPD, which made it possible to distinguish EGID from FAPD in children manifesting with a variety of GI symptoms.

Eosinophils are multifunctional cells that contribute to both innate and adaptive immunity, and are thereby involved in the initiation, propagation, and resolution of immune responses. When activated, eosinophils degranulate and release cytoplasmic granules, causing tissue damage and inflammation [16]. Accumulation and degradation of eosinophils in the GI tract may further cause neural stimulation and smooth muscle contraction, resulting in GI symptoms such as abdominal pain [17].

The diagnosis of EGIDs in clinical practice is complicated [18], as diagnosis requires invasive endoscopic biopsy of each of the involved GI segments; as such, there is an urgent need for noninvasive screening markers of EGID.

To date, an increase in peripheral eosinophil counts has been used as laboratory clue to detect EGID as peripheral eosinophilia has been observed in more than half of patients [9]. Furthermore, it has been suggested that peripheral eosinophilia may be beneficial in reflecting the presence of tissue eosinophilia in cases of EGID, although it was not useful in patients with FAPD [9,19]. However, the clinical significance of increased peripheral eosinophils is limited, as it can also be within normal range in other patients with EGID [20]. Furthermore, in our study, peripheral absolute eosinophil count or peripheral eosinophil percent did not show any significant differences between EGID and FAPD patients.

Other potential candidates for noninvasive markers of EGID include the cytotoxic granule proteins released by eosinophils. These granules primarily comprise the following four proteins; major basic protein, eosinophil peroxidase, eosinophil derived neurotoxin, and ECP. Of these

four granular proteins, ECP is the most well-known and has been used as a useful marker of asthma and other allergic diseases such as allergic rhinitis and atopic dermatitis [21-23].

The significance of measuring serum ECP has been analyzed in a previous study on adult EoE [24], while a recent pediatric study also reported that serum ECP was significantly higher in children with EoE than in the controls [25]. Although the significance of serum ECP as a noninvasive marker of EoE has been studied [24,25], no studies have so far evaluated the clinical significance of serum ECP as a noninvasive marker of EGIDs. In our study, when detecting EGID, serum ECP level beyond peripheral eosinophil counts was identified as a useful tool in pediatric patients. Serum ECP levels were also significantly higher in children and adolescents with EGID than in those with FAPD, although there were no differences in peripheral eosinophil counts. These results suggest that the increase in eosinophils in peripheral blood, as well as the increase in eosinophil activity, may play an important role in the pathogenesis of EGID. In addition, in our study, serum ECP levels significantly correlated with other laboratory markers such WBC, ESR, and peripheral eosinophil counts.

Finally, when the ROC analysis was applied to evaluate the diagnostic accuracy of serum ECP in children with EGID, the AUROC was 0.562 with an optimal cutoff 10.5 μg/mL, a sensitivity of 69.9%, and a specificity of 43.4%. Although the diagnostic accuracy of serum ECP for EGID was not sufficiently high in children, it still has some merits in practice as a screening test. In the absence of well-defined age-specific standards for serum ECP levels among children, these results could aid the assessment of EGID in pediatric patients. In addition, serum ECP may offer the convenience of easy measurement and a noninvasive diagnostic approach.

This study has several limitations which should be mentioned First, the retrospective single center design may be a limitation of the present study. Second, this study did not analyze the correlation between endoscopic- and histopathological features as well as tissue eosinophils. In the future, a comparison of serum ECP with tissue eosinophils as well as peripheral eosinophils may validate and further support the significance of serum ECP as a biomarker of EGID.

Nevertheless, this study has several strengths of this study. Firstly, this is the first pediatric study to investigate serum ECP measurement in EGIDs including all age groups from early childhood to adolescence. As all participants underwent endoscopic biopsies, histopathological evaluation was performed to confirm the diagnosis of EGID. Additionally, the inclusion of a large number of pediatric patients with endoscopic results allowed us to present a detailed study on pediatric EGID.

In conclusion, serum ECP level may be an useful noninvasive marker for differentiating EGID from FAPD in pediatric patients with chronic or recurrent GI symptoms when optimal cutoffs are applied. Future studies are required to identify and evaluate better noninvasive biomarker for the diagnosis and monitoring of pediatric EGIDs.

ACKNOWLEDGEMENTS

We would like to thank the Medical Research Collaborating Center of Seoul National University Bundang Hospital for the contributions in statistical analysis.

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