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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Eosinophil Count in Infants with Food Protein-Induced Allergic Proctocolitis

Besin Proteinine Bağlı Alerjik Proktokolitli İnfantlarda Eozinofil Sayısının Değerlendirilmesi

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ABSTRACT

Objective: The incidence of allergic proctocolitis due to food protein is increasing. Therefore, studies are needed to elucidate the pathophysiology of the disease as well as to identify simple, non-invasive markers. The aim of this study was to evaluate the relationship between the level of eosinophil in the blood and allergic proctocolitis.

Materials and Methods: The files of patients who were diagnosed with allergic proctocolitis at the Pediatric Allergy Outpatient Clinic of Başkent University's Faculty of Medicine, Ankara Hospital, between 2011 and 2021 were retrospectively reviewed. Three groups were formed according to eosinophil counts. Those with an eosinophil count below 400 10^3/μL were considered as the normal eosinophil group, those whose count was between 400-1499 10^3/μL were considered as the eosinophilia group, and those with 1500 10^3/μL and above were considered as the hypereosinophilia group.

Results: There were 108 patients diagnosed with allergic proctocolitis, of which 49.1% (n:53) were male. Of all the patients, 14.8% (n: 16) were in the hypereosinophilia group and 29.6% (n: 32) were in the eosinophilia group. Eosinophil elevation was more common in boys. There was no statistically significant difference in eosinophil count between those with single and multiple food allergies. It was observed that multiple food allergies were more common in babies older than two months (n:76) than in babies aged two months and younger (n:32) (p=0.031).

Conclusion: In our study, there was no difference between eosinophil levels and symptoms in infants with allergic proctocolitis. However, the importance of investigating multiple food allergies in the presence of eosinophilia in infants older than two months is clear.

Keywords: allergic proctocolitis, food allergy, eosinophil, infant

ÖZ

Amaç: Besin proteinine bağlı alerjik proktokolit görülme sıklığı artmaktadır. Bu nedenle hastalığın patofizyolojisinin aydınlatılmasının yanı sıra basit, invaziv olmayan belirteçlerin belirlenmesine yönelik çalışmalara ihtiyaç duyulmaktadır. Çalışmamızın amacı eozinofil düzeyi ile alerjik proktokolit arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: Başkent Üniversitesi Tıp Fakültesi, Ankara Hastanesi Çocuk Alerji polikliniğinde 2011-2021 yılları arasında alerjik proktokolit tanısı almış olan hastaların dosyaları retrospektif olarak incelendi. Eozinofil sayılarına göre üç grup oluşturuldu. Eozinofil düzeyi 400 10^3/μL altında olanlar normal eozinofil grubu, 400-1499 10^3/μL arası olanlar eozinofili grubu, 1500 10^3/μL ve üzeri olanlar hipereozinofili grubu olarak değerlendirildi. Çalışma Başkent Üniversitesi yerel etik kurulu tarafından onaylanan protokole uygun olarak yapıldı.

Bulgular: Alerjik proktokolit tanısı almış 108 hastanın %49,1'i (n:53) erkekti. Median yaş 3,5 (0,5-10) aydı. Tüm hastaların %14,8'i (n:16) hipereozinofili, %29,6'sı (n:32) eozinofili grubundaydı. Eozinofil yüksekliği erkek çocuklarda daha fazla görüldü (eozinofili grubunun %71,9'u, hipereozinofili grubunun %50'si erkekti). Gruplar arasında sadece anne sütü alan ile anne sütü ve formula mama alan infantlar açısından bir farklılık yoktu. Atopik dermatit, eozinofili grubunun %9,4'ünde, hipereozinofili grubunun da %5,9'unda mevcuttu. Sadece 56 hastaya deri prik testi uygulanmıştı. Deri prik testi sonuçlarına göre gruplar arasında anlamlı bir farklılık saptanmadı. Tekli ve çoklu besin alerjisi olanlar arasında eozinofil sayısı açısından istatistiksel olarak anlamlı fark yoktu. İki ay üstü bebeklerde (n:76) çoklu besin alerjisinin iki ay ve altı bebeklere (n:32) göre daha sık olduğu görüldü (p=0,031).

Sonuç: Çalışmamızda, alerjik proktokolitli bebeklerde eozinofil düzeyleri ile semptomlar arasında bir farklılık görülmedi. Ancak iki ay üstü bebeklerde eozinofili varlığında çoklu besin alerjisinin araştırılmasının önemini belirtmektedir.

Anahtar Kelimeler: alerjik proktokolit, besin alerjisi, eozinofil, ınfant

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INTRODUCTION

Food protein-induced allergic proctocolitis (FPAP) is a non-immunoglobulin E (IgE)-mediated food allergy that typically affects the rectosigmoid colon and presents with focal eosinophil infiltration in the lamina propria, increased intraepithelial CD8-positive T lymphocytes, focal mucosal erythema, and aphthous ulcerations (1). It presents with bloody , mucous stools in the first months of life. It mostly develops against cow's milk protein (97.7%), and secondly against egg (22%). More than one food allergy is observed in 34.1% of infants (2). Food allergy is seen in 0.5-1% of infants fed only with breast milk (3). A diagnosis of FPAP is made by taking the history of the patient, by clinical evaluation, and by an improvement in the patient's condition as a result of an exclusion diet. In infants fed with breast milk, foods that are thought to be allergens such as cow's milk and sometimes eggs and soya should be excluded from the mother's diet (1,2). Tolerance develops before the age of one in 40% of the patients, between 1-2 years in 27%, between 2-3 years in 9%, and after the age of 3 in 5% (4).

The incidence of FPAP is increasing (5). Therefore, studies are needed to elucidate the pathophysiology of the disease as well as to identify simple, non-invasive markers. In the literature, studies have been carried out on easy-to-calculate and non-invasive markers. There are studies evaluating the significance of values such as neutrophil/lymphocyte ratio (NLR), mean platelet volume, peripheral eosinophil count, specific IgE (sIgE) values, and positive skin prick test (SPT) in the diagnosis and follow-up of FPAP (1,2,4- 7). Again, higher eosinophil count, higher positive sIgE and positive SPT results were observed in infants with multiple food allergies compared to infants with single food allergies (2).

In light of this information, we wanted to evaluate the severity of clinical findings and the rates of eosinophilia and hypereosinophilia by examining the clinical features, laboratory tests, and especially the eosinophil count in the complete blood count of our patients diagnosed with FPAP. Every patient diagnosed with FPAP has eosinophilic infiltration in the lamina propria, but it is known that the level of eosinophils in the blood increases only in some patients. In particular, we sought to determine in which situations the eosinophil count can be used as a non-invasive marker by evaluating the relationship between the level of eosinophils and the severity of the proctocolitis clinic.

METHOD

The files of patients who were diagnosed with FPAP at the Pediatric Allergy Outpatient Clinic of Başkent University's Faculty of Medicine, Ankara Hospital, between 2011 and 2021 were retrospectively reviewed. Demographic information, age at diagnosis, complaints, presence of single or multiple food allergies, complete blood count, NLR, biochemical values, inflammatory markers, stool analysis, milk, and egg sIgE, and SPT values were examined from the files of the patients. Other causes of rectal bleeding such as infections, intussusception, volvulus, Hirschsprung's disease, and necrotizing enterocolitis were excluded. Three groups were formed according to eosinophil counts. Those with an eosinophil level below 400 10^3/µL were placed in the normal eosinophil group, those between 400-1499 10^3/µL were put in the eosinophilia group, and those with 1500 10^3/µL and above were placed in the hypereosinophilia group (8). The study was performed according to the protocol approved by the local ethics committee of Başkent University (KA 16/166).

Statistical Analysis

In the study, mean ± standard deviation or median (minimum-maximum) depending on assumptions were given for numerical variables as descriptive statistics, and number (n) and percentage (%) were given for categorical data. Analysis of Variance was used if parametric test assumptions were met in examining the difference between eosinophil groups. If not, the Kruskal-Wallis test was used. Pearson Chi-square test, Fisher's Exact test, or Fisher-Freeman-Halton Exact test were used in the evaluation of categorical data, depending on the assumptions. Spearman correlation coefficient and significance test were used to analyse the correlation between the two variables. $P<0.05$ was considered statistically significant in the analyses. The analyses of the study were made using the SPSS IBM v22 software platform.

RESULTS

In our study, 108 patients were evaluated, of which 49.1% (n:53) were male. The median age was 3.5 months (0.5-10 months). The median value of the complaint duration at presentation

Table 1: General characteristics by groups

	Normal eosinophil (n:60)	Eosinophilia (n:32)	Hypereosinophilia (n:16)	p
Boy	36.7% (22)	71.9% (23)	50% (8)	0.006[a]
Girl	63.3% (38)	28.1% (9)	50% (8)	
Age (month)	4 months (0.5-10)	3.25 months (1-7)	3.5 months (1-6.5)	0.438[b]
Prematüre birth	8.3% (5)	9.4% (3)	6.3% (1)	0.999[c]
Miad birth	91.7% (55)	90.6% (29)	93.8% (15)	
Time to diagnosis (day)	26.5 (1-150)	30 (1-150)	32.5 (3-130)	0.586[b]

a: Pearson Chi-square test; (n)%
b: Kruskal-Wallis test; Median (min-max)
c: Fisher-Freeman-Halton Exact test; (n)%

Table 2: Admission complaints by groups

Complaint	Normal eosinophil (n:60)	Eosinophilia (n:32)	Hypereosinophilia (n:16)	pa
Mucus poop	16.7% (10)	21.9% (7)	0% (0)	0.155
Bloody poop	76.7% (46)	65.6% (21)	93.8 % (15)	
Skin rash	5% (3)	6.3% (2)	0% (0)	
Unrest	1.7% (1)	0% (0)	0% (0)	
Diarrhea and rash	0% (0)	3.1% (1)	6.2% (1)	
Vomiting	0% (0)	3.1% (1)	0% (0)	

a: Fisher-Freeman-Halton Exact test; (n)%

Table 3: Laboratory results by groups

	Normal eosinophil (n:60)	Eosinophilia (n:32)	Hypereosinophilia (n:16)	p
Hemoglobin (g/dL)	11.9 (9.8-14.6)	11.3 (9.2-13.6)	11.9 (10.2-17.2)	0.213[a]
Mean corpuscular volume (fL)	80.4 (65.5-100.6)	82.25 (56.4-92.1)	79.3 (64.4-104.0)	0.720[a]
Platelets (10^3/µL)	386233±98152	418093±114925	420812±78180	0.249[b]
Neutrophil count (10^3/µL)	1960 (872.0-4950.0)	2010 (720-4370)	2430 (870-7510)	0.066[b]
Lymphocyte count (10^3/µL)	6160 (3380-10270)	6280 (1170-11400)	6810 (1240-10700)	0.250[b]
N/L rate	0.24 (0.21-0.32)	0.1950 (0.12-0.62)	0.94 (0.47-1.42)	0.194[b]
Total IgE (IU/mL)	3.98 (1.00-138.00)	2.75 (1.00-47.50)	2.73 (1.68-6.94)	0.835[b]

a: Analysis of Variance; Mean±Standard Deviation
b: Kruskal-Wallis test; Median(Minimum-Maximum)

was 28 days (1-150 days). Of all patients, 14.8% (n: 16) were in the hypereosinophilia group and 29.6% (n: 32) were in the eosinophilia group. Eosinophil elevation was more common in boys (p=0.006). 71.9% of the eosinophilia group and 50% of the hypereosinophilia group were male. The general characteristics of the patients are presented in Table 1.

The most common presenting complaint in all groups was bloody stool. There was no significant difference between the groups in terms of presentation complaints (p=0.155). The presenting complaints of the hypereosinophilia group were bloody stool (93.8%) and diarrhea with rash (6.2%). Arrival complaints by groups are presented in Table 2.

When the presence of allergy in the baby and/or family was evaluated, there was no significant difference between the groups (p=0.522). While the physical examination was normal in 78.1% of the patients, 18.1% had atopic dermatitis and 3.8% had an anal fissure. In addition, there was no difference in terms of eosinophilia between 'exclusively breastfed' and 'breastmilk and formula formula' infants (p=0.745). Atopic dermatitis was present in 9.4% of the eosinophilia group and 6.2% of the hypereosinophilia group. Those who received the rotavirus vaccine before diagnosis were 15.0% (n:9) in the group with normal eosinophilia, 25.0% (n:8) in the eosinophilia group, and 6.3% (n:1) in the hypereosinophilia group. There was no difference between these three groups in terms of rotavirus vaccination (p=0.227).

Laboratory values were compared. There was no difference between neutrophil count, platelet count, and NLR. Egg sIgE sensitivity was high in 5 patients and milk sIgE sensitivity was high in 4 patients. Only one patient had both milk and egg sIgE sensitivity. Total IgE was found to be high in one patient. There was no difference between the total IgE values measured. There was a weak positive correlation between eosinophil count and platelet levels (p=0.023, rs=0.219). Laboratory results are presented in Table 3.

No difference was found between the groups in stool occult blood (SOB) examination (p=0.651). SOB was positive in 41 patients. Of these patients, 22 (53.7%) were in the normal eosinophil group, 13 (31.7%) in the eosinophilia group, and 6 (14.6%) in the hypereosinophilia group. There were 68 patients for whom fecal-reducing substance (FRS) was tested. Patients with FRS (+) (n:17) had a significantly higher level of eosinophils than those with FRS(-) (n:51) (p=0.011). The number of patients with FRS (+) was 10 (58.8%) in the normal group, 2 (11.7%) in the eosinophilia group, and 5 (29.4%) in the hypereosinophilia group. The number of patients with FRS (-) according to the groups was 28 (54.9%) in the normal group, 20 (39.2%) in the eosinophilia group, and 3 (5.8%) in the hypereosinophilia group.

SPT was applied to 56 patients who did not respond to milk elimination. There was no significant difference between the groups in terms of SPT positivity (p=0.934). Egg positivity was

Table 4: Skin Prick Test results

	Normal eosinophil (n)	Eosinophilia (n)	Hypereosinophilia (n)	pa
Negative	**46.7% (14)**	**41.2% (7)**	**55.6% (5)**	
Milk	**6.7% (2)**	**17.6% (3)**	**0% (0)**	
Egg	**23.3% (7)**	**29.4% (5)**	**33.3% (3)**	
Milk and Egg	**3.3% (1)**	**0% (0)**	**0% (0)**	**0.934**
Nuts	**10.0% (3)**	**5.9% (1)**	**0% (0)**	
Egg and Nuts	**6.7% (2)**	**5.9% (1)**	**0% (0)**	
Egg, Nuts, Milk	**3.3% (1)**	**0% (0)**	**11.1% (1)**	

a: Fisher-Freeman-Halton Exact test; %(n)

the highest in all groups. In the hypereosinophilia group, one patient had positivity for milk and nuts (hazelnut, peanut, walnut, almond) other than eggs. The applied SPT and its results are presented in Table 4.

There was no difference in the frequency of single and multiple food allergies between the groups (p=0.115). Multiple food allergies were 40.0% (n:24) in the normal eosinophil group, 62.5% (n:20) in the eosinophilia group, and 43.8% (n:7) in the hypereosinophilia group.

It was observed that multiple food allergies were more common in infants over two months of age than in infants under two months of age (p=0.031). While 19.6% of infants with multiple food allergies were 2 months and younger, 80.4% were older than 2 months.

DISCUSSION

In our study, the aim of which was to evaluate the relationship between serum eosinophil levels and FPAP , 108 patients with a diagnosis of FPAP were evaluated retrospectively. Eosinophil elevation was evident in male infants. The most common complaint was bloody stool. There was no relationship between eosinophil values and the infant's diet, rotavirus vaccine, single or multiple food allergies, and family history of allergic disease. In addition, there was no difference in eosinophil levels according to the physical examination findings of the patients and the severity of the condition . We found that multiple food allergies were more common, especially in infants older than 2 months.

In FPAP, mucosal edema, focal epithelial erosions, and eosinophilic infiltration in the epithelium and lamina propria occur due to cell-mediated hypersensitivity in the distal region (3). Similar invasive and noninvasive methods are used in the diagnosis of allergic proctocolitis and other eosinophilic esophagitis and gastroenterocolitis with similar pathologies (9). One of the noninvasive tests frequently used by clinicians is blood eosinophil level (10). Every patient diagnosed with FPAP has eosinophilic infiltration in the lamina propria, but it is known that the number of eosinophils in the blood increases only in some patients (3,5,9). In a study conducted by Lozinsky et al., it was shown that 89.3% of 263 infants with FPAP had eosinophilic infiltration in the colonic mucosa and 43.8% had eosinophilia in the blood (11). Recent evidence also indicates dysregulation of specific cytokines in cases of eosinophilic gastroenterocolitis. Compared to normal controls, higher plasma concentrations of IL-5 and IL-15 were observed in these patients, which correlated with the blood eosinophil count (12). Therefore, it can be expected that eosinophil levels will also be increased in FPAP cases. However, since this increase is not observed in every patient, it is considered unnecessary for a definitive diagnosis (3). In our study, 32 (29.6%) of 108 patients had eosinophilia and 16 (14.8%) had hypereosinophilia. The eosinophil count was high in 44.4% of our patients. 71.9% of the eosinophilia group and 50% of the hypereosinophilia group were male. Similar to our study, some studies in the literature also found a higher rate of eosinophilia in males (9,13).

In our study the most common patient complaint was blood in stool in all groups. In fact, FPAP clinic often appears with the complaint of bloody or mucous stool (14). Other complaints were observed in our patients; bloodless mucus stool, skin rash, bloodless diarrhea with skin rash, vomiting, and restlessness. Similar to our patients, the findings in other studies regarding FPAP and other eosinophilic gastrointestinal diseases have features that fall between IgE-mediated food allergy and cell-mediated hypersensitivity (14). The distribution of complaints in our study was independent of eosinophilia levels. This suggests that there is no relationship between the level of eosinophilia and clinical symptoms and the severity of the disease. However, the small number of our patients may be a reason for not detecting this relationship.

In the physical examination findings of our patients, there were skin rash (n:19) and anal fissure (n:4) findings. Seven of the skin rashes were diagnosed as atopic dermatitis. Five of these patients had multiple food allergies, three had eosinophilia and one had hypereosinophilia. The physical examination findings of the patients did not differ according to the eosinophil groups. Consistent with our study, other studies are reporting that the frequency of skin allergies such as atopic dermatitis is significantly higher in FPAP patients than in the healthy population (15,16). None of our patients with anal fissure had constipation on physical examination. They also did not complain of bloody stools. In order to make a differential diagnosis of proctocolitis, both local treatments for anal fissures and elimination diet were performed. The

patients were followed up closely. After the anal fissure findings improved, it was observed that the complaints continued after exposure to cow's milk protein. Thus, the diagnosis of proctocolitis was confirmed.

Similar allergic disease findings were found in the family of 16% of eosinophilic gastrointestinal diseases (14). For this reason, it is thought that genetic and environmental factors interact together in the etiology. In the family history of these patients, 80% have atopic diseases and 62% have specific food sensitivities (14). In our study, 61 (56.4%) of 108 patients had a family history of allergic disease. Eosinophil levels did not differ between the groups in the presence of allergic disease in the family history.

The frequency of FPAP cases is thought to have increased after 1980, especially due to the more frequent use of cow's milk-based infant formulas (5). . In infants who are exclusively breastfed, FPAP occurs due to cow's milk protein and other proteins passed through the mother's diet.'

In our study, FPAP was found to be higher in infants receiving formula with breast milk (n: 61) compared to those receiving only breast milk (n: 47). Eosinophil levels were compared in both. No difference was detected.

FPAP may be misdiagnosed as mucus and occult blood may be seen in the stool after the rotavirus vaccine. In one study, side effects were compared between the oral rotavirus vaccine and the placebo group. The prevalence of fever, vomiting, and diarrhea is similar (17). In another retrospective study, it was observed that the prevalence of food allergy did not increase in children who were vaccinated with rotavirus compared to the general population. Again in this study, the prevalence of food allergy was found to be 1.76% until the 12-month follow-up after the rotavirus vaccine (18). In our study, 18 patients had a history of rotavirus vaccination. In our study, there was no significant difference in eosinophil levels between the groups compared to the rotavirus vaccine.

NLR is used to measure systemic inflammation. The relationship of NLR with some diseases such as heart disease, chronic diseases, and the Mediterranean fever has been shown in the literature (7). In studies investigating NLR values in allergic rhinitis and asthma, higher NLR values were found compared to the control group (19,20). In our study, no difference was found between the groups in neutrophil count and NLR values. There was a positive correlation between eosinophil count and platelet levels. Egg sIgE alone was high in 5 patients, and only milk sIgE was high in 4 patients. Both milk and egg sIgE was elevated in a single patient.

Stool microscopy (SM), SOB, and FRS tests, which are FPAP noninvasive diagnostic tests, rarely give positive results (15). One study evaluated the diagnostic validity of SOB in infants with rectal bleeding secondary to FPAP compared to healthy infants. Although SOB has sufficient sensitivity (84%; negative predictive value 83%), fecal occult blood specificity (66%; positive predictive value 68%) is insufficient because more than one-third of healthy infants are positive (21,22). It is not a reliable result that SM does not contain eosinophilia and occult blood, and there is no reducing substance in the stool. The routine use of these tests is not recommended (3). In our study, FRS was examined in 68 patients with SM, colic-type pain, and diarrhea in 77 patients, and no statistically significant results were found. In 7 patients with high eosinophilia (two in the eosinophilia and five in the hypereosinophilia group), there was a reducing substance in the stool.

In the literature, there are studies emphasising that IgE-mediated food sensitivity may exist in cases of proctocolitis (1). In the study of Çetinkaya et al., 204 patients were evaluated retrospectively. It was observed that 17 patients with IgE sensitivity to irritating foods at the initial evaluation had IgE sensitivity, and 7 patients developed IgE sensitivity in the follow-up. It has been noted that children with BPIAP may become sensitive to irritating foods over time and develop IgE-mediated allergies. In our study, sensitivity to a food was detected in 30 of 56 patients who underwent SPT. Egg sensitivity was the highest in all groups. In addition, there was sensitivity to egg, milk, and nuts (hazelnut, peanut, walnut, almond) in the form of single and multiple associations. These findings can be explained by the feeding habits of our babies and their mothers. Fifteen of 48 patients with an eosinophil level above 400 $10^3/\mu L$ had SPT positivity. When the SPT results were evaluated, no significant difference was found between the groups. Similar to sIgE levels, SPT results are of limited help in diagnosing FPAP, and usually negative or slightly positive test results are obtained (11). In our study, there was no difference between the groups in terms of the frequency of single and multiple food allergies. It was observed that multiple food allergies were more common in infants older than two months compared to infants under two months of age. Babies older than two months may become sensitized to foods over time. According to this result, the diagnosis of multiple food allergies should not be overlooked in patients older than 2 months.

The most important limitation of our study was that it was retrospective. Our laboratory evaluations were not complete for every patient. Having a larger number of cases would have increased the power of the evaluation. Despite all these limitations, we think that our study makes important contributions to the literature for the evaluation and follow-up of allergic proctocolitis cases with increasing incidence.

CONCLUSION

FPAP is one of the earliest signs of food allergies. Rectal bleeding is a benign disease manifested by symptoms such as mucus in the stool, increased frequency, and stool consistency. If there is a delay in the diagnosis when there is no bleeding in the stool, the tolerance may be delayed due to the prolongation of the period and the solution may be difficult with increased sensitivity to other allergens during complementary feeding. Or, with a misdiagnosis, the mother's breastfeeding is stopped, which creates health risks and may adversely affect the attachment process. Therefore, FPAP diagnosis and process management are important. Invasive methods should not be used unless

necessary at the stage of diagnosis. With a detailed anamnesis and physical examination, the process can be managed with the support of non-invasive methods. The results of our study do not support the use of eosinophilia as a predictor of the severity of the FPAP clinic, but they indicate the importance of investigating multiple food allergies in the presence of eosinophilia in infants over two months old. It would be useful to evaluate this issue with more cases and a prospective study.

Ethics Committee Approval: This study was approved by the ethics committee of the local ethics committee of Başkent University (KA 16/166).

Informed Consent: Informed consent was not obtained as it was a retrospective study.

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