Bloody Stool in Infants: A Pediatric Allergy View

İnfantlarda Kanlı Gayta: Pediatrik Alerji Bakışı

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ABSTRACT

Objective: The prevalence of food allergy (FA) has gradually increased. Bloody stool is among the symptoms associated with non-immunoglobulin E (IgE) mediated FA in infants. In our study, we shared the clinical characteristics of the patients who applied to our clinic with bloody stool.

Material and Methods: The data of the patients with bloody stool were reviewed. Patients' characteristics and the time of onset of tolerance in patients with FA were recorded, retrospectively.

Results: The 110 patient files were reviewed. 68% of the patients were diagnosed with FA (63 proctocolitis/12 enterocolitis), 22% with an anal fissure, and 9% with nonspecific colitis. The most common causative food was cow milk (57%), the second was the combination of egg and milk (24.2%), and the third was egg (18.2%). The presence of atopic dermatitis (AD) and eosinophil count at the time of admission did not affect tolerance development time but it was shown that skin prick test (SPT) positivity and the high level of total IgE at the time of admission delayed the development of tolerance [(p=0.02), (r=0.510, p=0.009)].

Conclusion: Bloody stool is one of the common complaints in infants. It does not always indicate a FA. The clinic is mild when the underlying disease is non-IgE mediated FA. However, accompanying IgE-type sensitivities negatively affect the prognosis. Elevated total IgE and SPT positivity at the time of diagnosis may give an impression that tolerance of baked products could be delayed in this type of allergy.

Key Words: Atopic dermatitis, Food allergy, Gastrointestinal hemorrhage, Infant, Proctocilitis

ÖZ

Amaç: Besin alerjisi (BA) sıklığı giderek artan bir hastalıktır. Kanlı gayta yakınması infantlarda non immunoglobulin E (IgE) aracılı BA ile ilişkilendirilen semptomlar arasındadır. Çalışmamızda kanlı gaita nedeniyle kliniğimize başvuran hastaların klinik özellikleri paylaşılmıştır.

Gereç ve Yöntemler: Kanlı gaitası olan hastaların verileri incelendi. Hastaların özellikleri ve BA saptanan hastalarda toleransın ne zaman geliştiği restrospektif kaydedildi.

Bulgular: 110 hastanın kayıtları incelendi. Bunlardan %68'i BA (63 proktokolit/12 enterokolit), %22'si anal fissür, %9'u nonspesifik kolit tanısı aldı. Şüpheli besin olarak en sık inek sütü (%57), ikinci sıklıkta yumurta ve süt birlikteliği (%24.2), üçüncü sıklıkta yumurta (%18.2) saptandı. Atopik dermatit (AD) olması, başvuru anındaki eozinofil sayısı tolerans zamanını

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etkilemezken deri prick test (DPT) pozitifliği ve başvuru anındaki yüksek total IgE düzeyinin toleransı geciktirdiği bulundu [(p=0.020), (r=0.510, p=0.009)].

Sonuç: Kanlı gaita, infantil dönemde sık karşılaşılan şikayetlerden biridir. Her zaman besin alerjisine işaret etmez. Altta yatan hastalık non-IgE kaynaklı BA olduğunda klinik ılımlıdır .Ancak eşlik eden IgE tipi duyarlılıklar prognozu olumsuz etkiler. Tanı anındaki total IgE yüksekliği ve DPT pozitifliği bu tip alerjilerde fırınlanmış ürün toleransının geç olacağı yönünde fikir verebilir.

Anahtar Sözcükler: Atopik dermatit, Besin alerjisi, Gastrointestinal hemoraji, İnfant, Proktokolit

INTRODUCTION

Food allergy (FA) is defined as an adverse food reaction which developed as a result of immune-mediated mechanisms. These mechanisms could be immunoglobulin E (IgE) mediated, cellular (non-IgE) and both IgE-mediated and cellular (mixed) (1). Although its prevalence increases worldwide, it varies between 2-8% among children (2).

Signs of non-IgE-mediated FAs occur from several hours to several days later after exposure. Symptoms are usually associated with the gastrointestinal system, such as blood in stool, vomiting, diarrhoea, abdominal discomfort and constipation. The most common food allergens are cow's milk, egg, soy and wheat in non–IgE-mediated FA (3). It is not always easy to distinguish these symptoms from other gastrointestinal system (GIS) diseases. Bloody stool in children is a common clinical problem; indeed, it is reportedly the presenting complaint for approximately 0.3% of children in the emergency department (4). In infants, allergic colitis and anorectal fissures represent the most common causes, besides, non-specific colitis, duplication of bowel, volvulus, Hirschsprung's disease, necrotizing enterocolitis and bleeding diathesis are the other causes of lower GIS bleeding (5). Bloody stool is a common finding in patients referred to pediatric allergy clinics. Food protein-induced allergic proctocolitis (FPIAP) was diagnosed from the presence of bloody stools or occult blood in 163 (18%) of 903 infants over a period of 3 years, and from the presence of occult blood alone in 63 (7%), in a recent prospective study (6). FPIAP is believed to resolve rapidly but a study of 257 infants with FPIAP in Turkey showed that 60% of children developed tolerance in the first year of life, although 99% did so within 3 years (7). SPT and specific IgE (sIgE) tests for food allergens are usually negative. However, about 20% of children with FPIAP may show sensitization or develop IgE-mediated allergy to offending foods over time (8).

In this study, laboratory and clinical characteristics of the patients who applied to and followed up in our clinic with bloody stool were reviewed.

MATERIALS and METHODS

File records of 110 patients were analysed who applied to our pediatric immunology and allergy outpatient clinic with bloody stool between January 2020-2021. Patients with chronic diseases and immunodeficiency were excluded from the study. Patients' demographic characteristics, accompanying findings, laboratory results, and time of the tolerance development in patients with FAs were recorded.

The infants with bloody stool and no accompanying complaints like weight loss, fever and whose symptoms disappeared with the elimination of suspected allergen from diet but whose symptoms reappeared with the addition of allergen to diet were considered FPIAP (3).

While infants who have profuse and repetitive vomiting 1-4 hours after food intake, followed by fatigue and lethargy were considered acute food protein-induced enterocolitis syndrome (FPIES), those with chronic diarrhea, intermittent vomiting, growth retardation, hypoalbuminemia, and anemia were considered as chronic FPIES (3).

Skin-prick tests (SPT) were performed in accordance with the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) using commercial extracts of the most common food allergens (ALK-Albello ®, Canada) such as cow's milk, eggs, soy, peanuts, and wheat flour. Such allergens were applied with a negative saline and positive histamine control (Histamindihydrochloride 0.1%) (9). Punctures were performed on the inner side of the forearm, on the allergen microdroplets using appropriate lancets. The reading was performed with a ruler graduated in millimeters after 15 minutes. The test result was considered negative with a wheal of <3 mm and positive with the wheal of ≥3 mm.

Atopy patch tests (APT) were performed on non-lesional, untreated skin of the back, in accordance with the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) (10). A technique similar to conventional patch tests have been used by performing atopy patch testing – IQ Ultimate TM (IQ-UL chambers,Chemotechnique MB,Vellinge,Sweden). The volume of each chamber was 32 µL and the inner area of the chamber was 64 mm^2. The APTs with native egg's white and yolk, peanuts, soy, cow's milk and wheat were applied. Wheat powder and soy powder were used with vehicle-distillated water (1 g of wheat powder or soya powder in 10 ml of distillated water), egg's white, yolk, cow's milk and peanuts were used in the native form as the fresh foods without any dilution. Single vehicle (distillated water) has been used as a negative control. The occlusion time of APTs was 48 h, the first results were evaluated 20 min after removal of the tests and the second results were analysed 72 h after the application of the tests. The APT results were graded according to European

Task Force on Atopic Dermatitis (ETFAD) standards (10): no reaction or erythema without infiltration (–), erythema and infiltration (+), erythema and few papules (++), erythema and many or spreading papules (+++), erythema, papules and vesicles (++++).

Statistics: The data were analyzed with SPSS 22.0. The Chi-square test and Fischer Exact Test were used for categorical variables. Numerical parameters were tested for normal distribution and the independent samples T-test was performed for pairwise group comparison and one-way Anova test was used for multi group comparisons among those normally distributed; and Mann Whitney U test was performed for pairwise group comparison and Kruskal Wallis test was used for multi group comparisons among those not normally distributed. $p < 0.05$ was considered statistically significant.

The study was approved by Dokuz Eylül University ethics committee with a decision number 2021/003-33 and with the date 01.02.2021.

RESULTS

The data of 110 patients were analysed and 75 of them (68%) were followed with the diagnosis of FA (63 proctocolitis/12 enterocolitis), 35 of them had no food allergy (32%); 25 had an anal fissure, and 10 had gastrointestinal complaints which are temporary and unrelated to food intake. These patients were considered as non-specific colitis. Statistical analyses were performed in patients who were diagnosed with FA (n:75). Fifty-two percent of the patients with FA were male, the median age of onset was 3 months, 74.7% were born with cesarean section and 14.7% were born prematurely. Sixty percent of them had atopic dermatitis (AD). The demographic data of patients were summarized in Table I. The causative food allergens in our study group and features of tolerance were summarized in Table II and Table III.

Table I: Clinical and laboratory data of patients.

Parameters	Median (25-75 per)
Age (month)	6 (5-10)
Age of onset of complaints (month)	3.2 (2-6)
Age of tolerance to baked products (n:28)	12 (8.2-14)
Follow-up duration of the patients (month)	10 (4-25)
Age of full tolerance (month) (n:17)	14 (12-20)
Total IgE (IU/ml) (n:65)	13.7 (5.3-38.5)
Eosinophil (%) (n:75)	3.3 (2.1-5)
Eosinophil (#) (n:75)	300 (200-500)
Specific IgE (kU/lt) (n:71)	0.23 (0-1.4)
Cow's milk (n:23,>0.35 kU/lt)	0 (0-0.55)
Egg positive (n:17,>0.35 kU/lt)	0 (0-0.31)
Patch test (n:27)	
Negative	23 (85.2)
Positive	4 (14.8%)
Skin prick test (n:66)	
Negative	39 (59.1)
Positive	27 (40.9%)
Tolerance (months)	
Baked products	12 (8-13)
Full tolerance	14 (11-18)
Formula	
None	42 (56)
Amino acid	21 (28)
Extensively hydrolyzed	12 (15)

Table II: Causative Food Allergens.

Causative Foods	n (%)
Cow's milk	42 (57)
Cow's milk + Egg	18 (24)
Egg	14 (18)
Others	
Cow's milk+ walnut	2 (2.7)
Cow's milk + egg+ wheat	2 (2.7)
Cow's milk +Sesame	2 (2.7)
Egg + Red meat	2 (2.7)
Egg + Banana	1 (1.4)

Table III: Comparison of cases by causative food allergens and features of tolerance.

	Cow's milk	Egg	Cow's milk+Egg	p
AD*				
Without	20(47)	0 (0)	7 (38)	0.013
With	22 (53)	14 (100)	11 (62)	
Age of onset of symptoms (months)†	3 (2-6)	4(2-5)	3.5 (2-6)	0.392
	Baked Tolerance	**Full Tolerance**		
SPT†				
Negative	9 (7.5-12)	12(10-18)		0.020
Positive	13 (12-16)	15.5 (13.5-27)		
AD*				
Without	21 (75)	13 (80)		>0.050
With	7 (25)	4 (20)		

AD: *Atopic dermatitis,* ***SPT:*** *skin prick test,* n(%), †median (25-75p)*

For patients with milk allergy and formula-fed, the type of formula used did not affect the age of onset of tolerance to baked products or full tolerance ($p > 0.050$). There was no significant relationship between the percentage of eosinophil and the time of tolerance to baked products or full tolerance ($p > 0.050$). We observed that there is a statistically significant positive correlation between mean total IgE value at admission and the mean age of tolerance to baked products ($r = 0.510$, $p = 0.009$) but no correlation between total IgE level and the mean age of full tolerance $p > 0.050$).

DISCUSSIONS

FA is a common disease and has an increasing prevalence among worldwide (1). On the other hand, bloody stool is not always associated with FAs. We presented 68% of patients have diagnosed with FA who applied to our clinic with the suspicion of non-IgE mediated FA and short-term follow-up data. We have showed that the most common food allergens were cow's milk and egg in infants presenting with bloody stools.

The symptoms of FPIAP generally start in the first weeks of life, while the clinical findings of FPIES generally vary with causative food (11,12). Although the clinical findings in our patients occured at a median of three months of age and minimum of two months of age.

AD was observed in 13% of the patients in a multicenter study conducted with FPIAP patients in our country, Turkey (7). FPIAP rate was found 60% in our patient group and it is quite higher than their rate. The pathogenesis of non-IgE and mixed-type food allergies are still unclear. It's known that the clinical course of FA varies from society to society and from region to region. AD is not only caused by a FA but could also be affected by many environmental factors. These factors may be the reason of this high rate that we have found.

Suspicious food allergens in FA are affected by the nutritional habits of societies (2). In parallel to many studies conducted in our country, the most common causative food in our study was cow's milk protein followed by egg protein (7,14-16).

Formulas are not recommended to more than half of the patients with cow's milk protein allergies. Due to varying breastfeeding rates in several countries, formula-fed infants' rate has been affected. The age of tolerance to baked products was not different in formula fed infants compared to breastfed infants (p=0.445). Breast feeding is still preferred primarily rather than formulas in infants with FA. Formula feeding does not play an essential role in improving the prognosis of the disease (17).

The prognosis of non-IgE mediated FA is generally favourable and non-IgE FAs usually resolve between the ages of three to five before the school-age (18). FPIAP generally resolves at the ages of 1-2 years. In a study with large sample size, infants were able to consume cow's milk protein at the age of 11 months (6). Tolerance ages in our study were compatible with the literature and the median age of baked food tolerance was found to be 12 months (8-13 months) and the median age to end all extensive elimination diets was 14 months (12-20 months).

Egg sensitivity is closely related to AD, especially in infants who developed AD in their first year of life (19). AD was presented in all patients with egg allergy and in 52.8% of patients with milk allergy (p = 0.013). The prognosis of the disease is not affected by accompanying AD and there was no statistically significant difference between patients with AD (12 [9-13.8] months) and without AD in terms of the mean age of tolerance to baked products (p = 0.592).

IgE-mediated FA tends to be persistent (7). Our data also supported this view in our study and food tolerance time was significantly delayed in the patients who have positive SPTs compared to negative SPTs (p = 0.020). Although our study group included patients with non-IgE mediated FAs like FPIAP and FPIES, positive SPT results were presented in 40.9% of patients (n = 27). The SPT positivity rate may have been high due to patients with AD in our study group. AD is classified under mixed-type reactions with findings of FA and SPT positivity may be seen (2).

In our study which we analysed parameters that could predict prognosis, it was determined that the higher the total IgE at admission had positive correlation with delayed tolerance (r=0.510, p=0.009). Although total IgE is accepted as a biomarker for allergic disease, it has not proven an influence on the prognosis of FA (20). The applicability of these results to the general population was limited, as it is a study based on single center experiences and included only patients presenting to a tertiary health care center. It should be studied with larger sample sizes.

CONCLUSION

There are still many unknowns in non-IgE mediated FAs. It should be kept in mind that not all infants with bloody stool have a FA. In infants with bloody stool who have FA diagnosis, the most common food allergens are cow's milk and eggs. Non-IgE mediated FAs have a favourable prognosis, but IgE-type sensitizations have negative effect on the prognosis. Total IgE level at the admission and a positive SPT may help predicting the prognosis.

REFERENCES

1. Labrosse R, Graham F, Caubet JC. Non-IgE-Mediated Gastrointestinal Food Allergies in Children: An Update. Nutrients 2020;12:2086.
2. Cianferoni A. Non-IgE Mediated Food Allergy. Curr Pediatr Rev 2020;16:95-105.
3. Meyer R, Chebar Lozinsky A, Fleischer DM, Vieira MC, Du Toit G, Vandenplas Y, et al. Diagnosis and management of Non-IgE gastrointestinal allergies in breastfed infants-An EAACI Position Paper. Allergy 2020;75:14-32.
4. Osman D, Djibré M, Da Silva D, Goulenok C. Management by the intensivist of gastrointestinal bleeding in adults and children. Ann Intensive Care 2012;2:46.
5. Romano C, Oliva S, Martellossi S, Miele E, Arrigo S, Graziani MG, et al. Pediatric gastrointestinal bleeding: Perspectives from the Italian Society of Pediatric Gastroenterology. World J Gastroenterol 2017; 23:1328-37.

6. Martin VM, Virkud YV, Seay H, Hickey A, Ndahayo R, Rosow R, et al. Prospective Assessment of Pediatrician-Diagnosed Food Protein-Induced Allergic Proctocolitis by Gross or Occult Blood. J Allergy Clin Immunol Pract 2020;8:1692-9.e1.
7. Buyuktiryaki B, Kulhas Celik I, Erdem SB, Capanoglu M, Civelek E, Guc BU, et al. Risk Factors Influencing Tolerance and Clinical Features of Food Protein-induced Allergic Proctocolitis. J Pediatr Gastroenterol Nutr 2020;70:574-9.
8. Cetinkaya PG, Ocak M, Sahiner UM, Sekerel BE, Soyer O. Food protein-induced allergic proctocolitis may have distinct phenotypes. Ann Allergy Asthma Immunol 2021;126:75-82.
9. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test - European standards. Clin Transl Allergy 2013;3:3.
10. Turjanmaa K, Darsow U, Niggemann B, Rance F, Vanto T, Werfel T. EAACI/GA2LEN position paper: present status of the atopy patch test. Allergy 2006;61:1377-84.
11. Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome and allergic proctocolitis. Allergy Asthma Proc 2015; 36:172– 84.
12. Caubet JC, Ford LS, Sickles L, Järvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol 2014;134:382-9.
13. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. Immunol Allergy Clin North Am 2015;35:161-83.
14. Arik Yilmaz E, Soyer O, Cavkaytar O, Karaatmaca B, Buyuktiryaki B, Sahiner UM, et al. Characteristics of children with food protein-induced enterocolitis and allergic proctocolitis. Allergy Asthma Proc 2017;38: 54-62.
15. Sirin Kose S, Asilsoy S, Uzuner N, Karaman O, Anal O. Outcomes of Baked Milk and Egg Challenge in Cow's Milk and Hen's Egg Allergy: Can Tolerance Be Predicted with Allergen-Specific IgE and Prick-to-Prick Test?. Int Arch Allergy Immunol 2019;180:264-73.
16. Guler N, Cokugras FC, Sapan N, Selimoglu A, Turktas I, Cokugras H et al. Diagnosis and management of cow's milk protein allergy in Turkey: Region-specific recommendations by an expert-panel. Allergol Immunopathol (Madr) 2020;48:202-10.
17. Ahmadipour S, Najafi M, Motamed F, Rahmani P. Feeding-based treatment of allergic proctocolitis and associated clinical outcomes. Clin Nutr ESPEN 2020;40:237-41.
18. Caubet J, Cianferoni A, Groetch M, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome. Clin Exp Allergy 2019:9:1178–90.
19. Čelakovská J, Bukač J, Vaňková R, Krejsek I, Krcmova C. Andrýs. Egg allergy in atopic dermatitis patients-analysis of results of specific extract IgE and specific IgE to molecular components. Bird-egg syndrome, Food Agric Immunol 2021;32:265-82.
20. Cetinkaya PG, Kahveci M, Karaatmaca B, Esenboga S, Sahiner UM, Sekerel B, et al. Predictors for late tolerance development in food protein-induced allergic proctocolitis. Allergy Asthma Proc 2020;41:11-8.