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The effect of formula type on the prognosis of allergic proctocolitis due to cow's milk allergy

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Abstract
Background: Food protein-induced allergic proctocolitis is a nonimmunoglobulin E-mediated, self-limited food allergy of the rectum and the colon. Cow's milk protein is the most common allergen responsible for the disease.
Objective: This study aimed to investigate the roles of different types of formulas in building early tolerance to food protein-induced allergic proctocolitis in infants.
Methods: The medical records of 45 pediatric patients diagnosed with proctocolitis due to cow's milk allergy between August 2021 and August 2023 and whose disease progression was followed in three tertiary care centers were reviewed retrospectively.
Results: The study included 45 patients who were diagnosed with proctocolitis due to cow's milk allergy (24 males, 21 females; median age: 4 months). Among them, 24 patients were fed an amino acid-based formula, and 21 (46.7%) patients were fed an extensively hydrolyzed formula. The average age of acquisition of cow's milk tolerance was lower in the group fed with the amino acid-based formula than in the group fed with extensively hydrolyzed formula (P = 0.038). Furthermore, the group fed with amino acid-based formula had a shorter tolerance period than the group fed with the extensively hydrolyzed formula group (P = 0.044).
Conclusion: Compared to an extensively hydrolyzed formula, an amino acid-based formula led to the early development of tolerance in children with allergic proctocolitis induced by cow's milk.

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Introduction

Cow's milk (CM) allergy is the most common childhood food allergy in the world, with a prevalence rate of 1.9–4.9%.[1] Food protein-induced allergic proctocolitis (FPIAP) is a non-immunoglobulin E (IgE)-mediated, self-limited food allergy of the rectum and the colon.[2] Its symptoms typically begin in the first months of life and, in most cases, resolve by 15 months to 2.5 years of age. Infants with FPIAP usually present with red blood and mucus in stool, with or without diarrhea. While some may be fussy and irritable, most are generally well-appearing infants. Their physical examinations and weights tend to be normal.[3] FPIAP is diagnosed based on only an elimination diet or a histological criterion; the elimination diet may be followed by reintroduction to the diet. The elimination diet method is essential for treating allergic enteritis. Gross rectal bleeding should resolve within 72–96 h, but the total resolution of symptoms takes 1–2 weeks from the beginning of the diet. Factors that affect tolerance include nutrition, breastfeeding, and environmental factors, but these have not been extensively studied.[4]

Breastfeeding is the most complete alternative for infants with cow's milk protein allergy (CMPA) for adequate growth and development, and a milk protein elimination diet is the treatment of choice for the control of clinical manifestations. In exclusively breastfed infants, FPIAP is caused by food proteins derived from the maternal diet, usually CM, with the allergen protein passing into the breast milk. In some cases, multiple food allergies can occur.[5] An infant who requires breast milk substitutes should be given a hypoallergenic formula. This can be a formula with extensively hydrolyzed proteins (EHF) or an elemental formula based on free amino acids (AAF). EHFs are generally used as the first-line treatment for mild and moderate CMPA.[6]

This study aimed to investigate the roles of different types of formulas in building early tolerance to FPIAP in infants.

Materials and Methods

We retrospectively reviewed the electronic medical files of children diagnosed with proctocolitis upon being evaluated by the Pediatric Immunology and Allergy Clinic of Istanbul Başakşehir Çam and Sakura City Hospital, the Inonu University Medical Faculty, and Istanbul Cemil Tascioglu City Hospital between August 2020 and August 2023. Patients whose oral provocation tests showed the development of complete tolerance to cow's milk protein were included in the study. Specifically, patients who did not develop any gastrointestinal symptoms for 4 weeks after their oral provocation test were considered to have developed tolerance. A questionnaire form was filled out for each patient, including information on the patient's age of diagnosis, age of tolerance, gender, breastfeeding duration, length of tolerance, type of formula, dietary pattern, clinical findings, comorbid atopic disease, and familial atopic disease. Laboratory data, such as skin prick test results, eosinophil levels, serum total IgE levels, serum-specific IgE levels against suspected allergens, and provocation test results, were obtained from the electronic patient files.

This study was approved by the Ethics Committee of the Başakşehir Cam and Sakura City Hospital (File number: KAEK/2023-507).

Statistical analysis

The study data were analyzed using SPSS 22. Descriptive statistics were presented as numbers and percentages for categorical variables and as mean ± standard deviation values or medians (least maximum values) for numerical variables. The presence of a normal distribution was determined using histograms, Q–Q plots, and normal distribution tests (the Kolmogorov–Smirnov test or Shapiro–Wilk test). Categorical variables were described using Pearson's chi-square test; if assumptions were not met, comparisons were done using Fisher's exact test. For nonparametric numerical variables in two independent groups, the Mann–Whitney U test was used. P-values < 0.05 were considered statistically significant.

Results

The study included 45 patients who were diagnosed with proctocolitis due to CM allergy (24 males, 21 females; median age: 4 months). A comorbid atopic disease was present in 31 (68.9%) patients. Twenty-four patients were fed an AAF (14 males; median age: 4 months), and 21 (46.7%) patients were fed an EHF (10 males; median age: 4 months). The patients' demographic characteristics are summarized in Table 1.

The age of CM tolerance acquisition was lower in the AAF group than in the EHF group (P = 0.038). Furthermore, the tolerance period was shorter in the AAF group than in the EHF group (P = 0.044). The rates of breastfeeding (P = 0.025) and familial atopic disease (P = 0.012) were also higher in the AAF group. There were no statistically significant differences between the two groups in terms of age at diagnosis, gender, comorbid atopic disease, time to start complementary food, baseline and posttreatment serum eosinophil levels, and baseline and posttreatment serum total IgE levels (P > 0.05). The results are summarized in Table 2.

Discussion

FPIAP is a non-IgE-mediated, self-limiting food allergy localized in the colon and the rectum. It usually occurs early in life, and patients present with blood-streaked and/or mucus-containing stools. Breastfed infants are usually affected at an older age and show milder histological findings. Infants tend to appear well but may exhibit colicky behavior with increased bowel movements.[2] FPIAP treatment includes 2–4 weeks of an elimination diet that involves removing CM protein from the mother's diet if breastfeeding (first-line treatment) and the usage of a hypoallergenic formula.[7] Hypoallergenic formula usage is preferred when FPIAP is suspected in infants who are not breastfed. There are two types of hypoallergenic formulas: EHF and AAF. Guidelines recommend EHF as the first-choice formula for

Table 1 Characteristics of children with proctocolitis.

	n (%)
Age of symptom onset, month, median (min-max)	2 (1-7)
Age of diagnosis, month, median (min-max)	4 (1-8)
Age of tolerance, month, median (min-max)	12 (7-24)
Length of the tolerance time, month, median (min-max)	8 (2-19)
Gender, male	24 (53.3)
Breastfeeding	
<6 months	14 (22.5)
>6 months	31 (77.5)
Clinical findings	
Blood and mucus in stool	45 (100.0)
Abdominal pain/discomfort	18 (40.0)
Diarrhea	15 (33.3)
Constipation	12 (26.7)
Vomit	6 (13.3)
Comorbid atopic diseases	31 (68.9)
Atopic dermatitis	16 (35.6)
Astım/recurrent wheezing	10 (22.2)
Allergic/persistent rhinitis	4 (8.9)
Drug allergy	1 (2.2)
Familial atopy	26 (57.8)
Eosinophilia at onset	17 (37.8)
Eosinophilia level at onset, median (min-max),	3.2 (0.1-10.9)
Eosinophilia at the end of the disease	13 (28.9)
Eosinophilia level at the end of the disease, median (min-max)	2.5 (0.1-9.8)
High serum total IgE at onset	6 (13.3)
Serum total IgE level at, onset median (min-max), IU/mL	4.8 (0.2-463)
High serum total IgE at the end of the disease	11 (24.4)
Serum total IgE level at the end of the disease, median (min-max), IU/mL	29.8 (1.0-350.0)
Type of formula	
Amino acid-based	24 (53.3)
Extensively hydrolyzed	21 (46.7)
Dietary pattern	
Breast milk and formula	29 (64.4)
Formula	16 (35.6)
Time to start complementary food, month	
Five	10 (22.2)
Six	29 (64.4)
Seven	4 (8.9)
Eight	1 (2.2)
Unknown	1 (2.2)
Total	45 (100.0)

the treatment of CMPA, except in cases involving special conditions, such as faltering growth or failure to thrive, multiple food allergies, eosinophilic esophagitis, food protein-induced enterocolitis, severe eczema and anaphylaxis, and lack of symptom improvement with EHF.[8-10]

AAF is a formula containing free synthetic amino acids. Its most important feature is that it does not contain residual CM allergens. In contrast, EHF contains bioactive peptides that may cause allergic responses. Peptides with molecular weights less than 1200 Da have been reported to be suitable for the treatment of CM allergy in children.[10] EHF formulas contain short peptides of less than 1500 Da.[11] In previous tolerance studies comparing an AAF and an EHF in children with non-IgE-mediated CM allergy, a greater regression of gastrointestinal symptoms was found in patients on an AAF.[12-14] In this study, the tolerance period was found to be shorter in infants fed an AAF than in infants fed an EHF. In previous studies involving severe complex gastrointestinal manifestations of non-IgE-mediated food allergies (i.e., enterocolitis or proctitis syndromes with faltering growth and eosinophilic gastrointestinal disorders), better results were obtained with AAF than with EHF.[9] Because the pathophysiology of non-IgE-mediated food allergies is not fully understood, it is not easy to evaluate our results.[2]

Table 2 Comparison of the type of formula on the prognosis of proctocolitis due to cow's milk allergy.

	Amino acid-based formula n (%)	Extensively hydrolyzed formula n (%)	P
Age of diagnosis, month, median (min-max)	4 (1-7)	4 (2-8)	0.963
Age of tolerance, month, median (min-max)	12 (8-24)	14 (7-24)	**0.038**
Length of the tolerance period, month, median (min-max)	8 (2-18)	10 (5-19)	**0.044**
Time to start complementary food, month	6 (5-7)	6 (5-8)	0.499
Gender, male	14 (58.3)	10 (47.6)	0.472
Breastfeeding (>6 months)	20 (83.3)	11 (52.4)	**0.025**
Comorbid atopic diseases	16 (66.6)	15 (71.4)	0.783
Familial atopy	16 (66.6)	8 (38.1)	**0.012**
Eosinophilia at onset	9 (37.5)	8 (38.1)	0.987
Eosinophilia level at onset, median (min-max)	3.5 (0.2-8.2)	2.0 (0.1-10.9)	0.387
Eosinophilia at the end of the disease	8 (33.3)	5 (23.8)	0.482
Eosinophilia level at the end of the disease, median (min-max)	2.5 (0.3-6.0)	2.4 (0.1-9.8)	0.820
High serum total IgE at onset	3 (12.5)	3 (14.3)	0.860
Serum total IgE level at, onset median (min-max), IU/mL	15.0 (0.2-463.0)	3.5 (1.0-150.0)	0.168
High serum total IgE at the end of the disease	8 (33.3)	3 (14.3)	0.515
Serum total IgE level at the end of the disease, median (min-max), IU/mL	65.0 (1.0-350.0)	21.0 (3.6-232.0)	0.122
Total	24 (100.0)	21 (100.0)	

Bold = statistically significant.

It is generally accepted that the initiation time and duration of breastfeeding have a protective effect against atopy in general and CM protein allergy in particular.[15] Contact with formula usually occurs sooner in non-IgE-mediated cases than IgE-mediated cases, and breastfeeding is consequently abandoned earlier because of perceived gastrointestinal symptoms.[16] The composition of milk content in breastfed infants varies. Cytokines or immunoglobulins present in breast milk may lead to the development of tolerance to antigens found in breast milk.[17] In the study by Arvola et al., which involved infants with allergic proctocolitis due to CM, one group of patients was fed a CM-free diet (mother and infant) while the other group was fed a normal diet.[18] It was observed that recovery from rectal bleeding occurred faster in infants who received the CM-free diet than in infants who received a normal diet. A recent systematic review found that allergic proctocolitis occurred before the age of 1 in a majority of infants whose mothers were on a CM-free diet.[19] In the study by Pumberger et al., 10 out of 11 patients with FPIAP whose mothers received a diet free of CM protein recovered within 3-4 days.[20] In this study, the rate of breastfeeding was higher in the group fed the AAF than in the group fed the EHF, which may have contributed to the earlier development of tolerance in the former group.

The findings by Çetinkaya et al. support the theory that an early introduction of complementary feeding accelerates tolerance in FPIAP patients.[21] In the present study, there was no significant difference between the AAF and EHF groups in terms of feeding time with complementary food. However, the tolerance time was shorter in the AAF group than in the EHF group. In the study by Çetinkaya et al., the median time to start complementary feeding was 5.5 months, and the median tolerance time was 11 months. In the present study, the median time to start complementary feeding was 6 months, while the median tolerance time was 12 and 14 months in the AAF and EHF groups, respectively.

The present study had a few limitations that may have affected its results. Firstly, only a small number of patients were included in the study. This may be attributed to the recent difficulties experienced by patients in our country in temporarily accessing EHFs. The second limitation of the study was its retrospective design. This may have resulted in some missing data.

Conclusion

The current guidelines for CM protein allergy recommend EHF as the first choice, except in some special situations (anaphylaxis, eosinophilic esophagitis, etc.). The current guidelines (DRACMA, BSACI, and ESPGHAN) also recommend EHF as the first choice for allergic proctocolitis.[9] In our study, AAF resulted in better tolerance times than EHF in cases of CM-induced allergic proctocolitis.

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None.

Author Contributions

All authors contributed to the data collection, analysis, and interpretation. MHC contributed to the conception and design of the study, and supervision. SN and MHC prepared the draft manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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