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The Frequency of Atopic Dermatitis and Other Skin Manifestations in Infants with Cow's Milk Protein Allergy in Karabük, Turkey

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Abstract

Background

Atopic dermatitis (AD) is the most common skin disease in childhood, and Cow's milk protein allergy (CMPA) is the most common cause of food allergies in infancy and may be characterized by atopic dermatitis with skin involvement as the first finding. The aim of this study is to determine the serum eosinophil cationic protein (sECP) levels, eosinophil counts and the frequency of AD and other skin manifestation among infants with CMPA.

Materials and Methods: This cross-sectional study was conducted in Karabük province, Turkey. Eighty-three infants who were diagnosed with CMPA and followed at the Karabük Training Hospital Pediatric outpatient clinic. The first group consisted of 52 infants presenting with skin manifestations. The second group consisted of 31 infants who were not presenting skin manifestations. The sECP level of infants in both groups was measured using an Immulite 2000 XPi analyzer Immunoassay System (Germany).

Results: Of 83 infants with CMPA, 62.6% (n=52) were detected skin involvement as the first finding. The proportions of atopic dermatitis and urticaria in CMPA infants with skin involvement were 90.4% and 9.6% respectively. The median sECP level and eosinophil counts (56.5 ng/mL vs 470/mm^3, p-value=0.001), in skin manifestations with CMPA group were significantly higher than that in the CMPA group without skin manifestations (33.1 ng/mL vs. 270/mm^3, p-value=0.006).

Conclusion

This study revealed that AD is the most common skin manifestation of CMPA and also found higher sECP levels in infants with skin involvement. The frequency of both diseases, which are easily treated with elimination diet, is increasing day by day.

Key Words: Atopic dermatitis, Cow's milk, Eosinophil, Infant, Protein allergy, Turkey.

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1- INTRODUCTION

Food allergies are the totality of adverse reactions to foods involving multiple systems, ranging from mild clinical symptoms to serious life-threatening reactions that occur with the activation of the immune system. This process includes IgE-mediated (hypersensitivity) reactions, non-IgE-mediated (cell-mediated) reactions, and mixed-type reactions involving both reaction types depending on the immunopathology (1). Cow's milk protein allergy (CMPA) is the most common cause of food allergies in the infantile period. Characterized by an inflammatory reaction caused by immunological mechanisms against milk proteins, CMPA affects 1.8% to 7.5% of infants (2-5).

Genetic factors are involved in the development of food allergies, and infants with a family history of allergies are known to be at higher risk for this disease (6-8). Even though detailed medical history, diagnostic elimination diets, skin prick tests, serum eosinophilic cationic protein level (sECP), and specific IgE measurements are helpful for diagnosis of CMPA (9). Considering that multiple systems are affected depending on the pathophysiological mechanism and the severity of the immunological reaction, CMPA manifests itself with a wide range of clinical signs and symptoms (10-12).

Of the patients, clinically, 50-70% present with skin findings such as atopic dermatitis (AD), and urticaria, 50-60% with gastrointestinal symptoms such as bloody diarrhea and vomiting, and 20-30% with respiratory system symptoms such as wheezing (12). AD is the most common chronic inflammatory skin disease in children, affecting 17-24% of children and 4-7% of adults (13, 14). Increased permeability to food allergens due to genetic predisposition, environmental triggers and deterioration of skin barrier function are involved in the development of AD. Food allergies play an important role in the etiology of AD, and CMPA is the most common food allergy in the infantile period (15-18). Various criteria have been developed over the years to facilitate the diagnosis of AD. The Hanifin-Rajka criteria are comprehensive and are generally considered as the golden standard for the diagnosis of AD (19, 20). The criteria of the UK Working Group (UKWP), essentially an abbreviated version of the Hanifin-Rajka criteria, are more useful for diagnosis in children rather than in adults (21). The diagnosis of AD is determined according to the UKWP and Hanifin-Rajka criteria, while its severity is classified according to the "Scoring Atopic Dermatitis" (SCORAD) index (17, 19).

The main purpose of the present study was to determine the frequency of atopic dermatitis and other skin manifestations among infants with CMPA. Second purpose of the study was to investigate the sECP levels, eosinophil counts and clinical features in CMPA infants with and without skin manifestations. To our knowledge, this is the first study in Turkish CMPA infants to investigate the the frequency of skin manifestations among infants with CMPA and to simultaneously evaluate their sECP levels.

2- MATERIALS AND METHODS

2-1. Study design and population

This cross-sectional study was carried out at the Department of Pediatric Gastroenterology, Karabuk Training and Education Hospital, Turkey, between January and December 2019. Eighty-three infants with CMPA defined by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Guideline: Diagnosis and Management of CMPA, aged 1 -12 months, were included in the presented study (4).

2-2. Methods

Infants with CMPA were divided into two groups. The first group consisted of 52 infants presenting with skin manifestations. The second group consisted of 31 infants that did not present with skin manifestations. Infants with CMPA were evaluated according to Hanifin-Rajka criteria (19) in terms of the presence of skin findings regardless of the severity of Atopic dermatitis (AD).

2-3. Laboratory measurements

For the eosinophil and whole blood count, blood was collected in 2-mL, ethylenediaminetetraaceticacid (EDTA) anticoagulant tubes and analyzed by using a Beckman Coulter LH 780 analyzer. The sECP level was measured using an Immulite 2000 XPi analyzer Immunoassay System (Germany).

2-4. Ethical consideration

The study was approved by the Ethics Committee for Non-invasive Clinical Research of Karabuk University, under No. 2020/209.

2-5. Inclusion and exclusion criteria

The inclusion criteria included infants with CMPA aged 1-12 months old.The exclusion criteria included infants with genetic, metabolic, infectious diseases, anatomical disorders in gastrointestinal tract and multiple food allergies except CMPA.

2-6. Data Analyses

The data were analyzed with SPSS version 21.0 software for Windows. Results are expressed as mean (SD) or median (range). Kolmogorov–Smirnov test was carried out to determine the normality of data distribution. Values of age, ECP and eosinophil count had abnormal data distribution, by Kolmogorov-Smirnov test ($p<0.05$), therefore, median values (interquartile range) between groups were determined and compared using Mann-Whitney U test. Correlation analyses were evaluated with Spearman's correlation test. A p-value of less than 0.05 was considered to be statistically significant.

3- RESULTS

Eighty-three infants with CMPA were included in the study and 52 (62.6%) infants detected skin involvement as the first finding. The median age of infants was 6 (1-12) months. Positive family history of allergy was reported in 31 (37.3%) of infants. The demographic and nutritional characteristics of the cases are shown in the **Table.1**. With regard to complaints, 52 (62.6%) presented with skin manifestation, 47 (56.6 %) from hematochezia, 27 (32.5%) from vomiting and 9 (10.8%) wheezing. The median age of 83 infants with CMPA (46 males, 55.4%), and 52 infants with skin manifestations with CMPA (27 males, 51.9%) were 6 (1-12) and 6 (2-12) months, respectively. There were no statistically significance differences between the two groups with respect to age, gender, height, weight and nutritional characteristics.

The median ECP and eosinophil counts of all patients enrolled into the study were found to be 44(4-220) ng/mL and 400(30-1720) /mm^3, respectively. The median sECP level and eosinophil counts [56.5 (4-220) ng/mL vs 470 (30-1720) /mm^3], in the skin manifestations with CMPA group were significantly higher than that in the CMPA group without skin manifestations [33.1 (14.4-56.8) ng/mL vs 270(110-960) / mm3] (**Tables 1, 2**). In the CMPA group with skin manifestations, the sECP level was positively correlated to eosinophil count (p=0.001). But there was no correlation between sECP and eosinophil counts in the other group (p=0.127) (**Table.3**).

Table-1: Demographic and clinical characteristics of infants included in this study.

Variables	Number	%
Gender		
- Male	46	55.4
- Female	37	44.6
Age (months)	6 (1-12)	
Body height (cm) (P25-P75)*	68 (47.5-80.5)	
Body weight (gr) (P25-P75)	7900 (3550-12250)	
Time of beginning complementary food (months)	5±1	
Family history of allergy	31	37.3
Feeding type		
- Breastmilk	40	48.2
- Breastmilk + formula	39	47
- Formula	4	4.8
Skin symptoms		
- Atopic dermatitis	47	90.4
- Urticaria	5	9.6
Time of appearance of skin findings (months)	5 (2-11)	
Gastrointestinal symptoms		
- Vomiting	27	32.5
- Rectal bleeding	47	56.6
Respiratory symptoms		
- Wheezing	9	10.8
Median ECP** (ng/ml) (P25-P75)	44 (4-220)	
Median Eosinophil count (mm3) (P25-P75)	400 (30-1720)	
Percentage of Eosinophil	3.7(0.4-18.3	

*P25-P75: Median values, **ECP: Eosinophil cationic protein.

Table-2: Demographic and laboratory characteristics in infants with and without skin manifestation.

Variables	Infants with skin manifestation, Number (%)	Infants without skin manifestation, Number (%)	P-value
Number (%)	52(62.6)	31(37.4)	0.000
Gender			
- Male	27 (51.9)	19 (61.3)	>0.05
- Female	25 (48.1)	12 (38.7)	>0.05
Age (months)	6 (2-12)	7 (1-12)	>0.05
Body height (cm) (P25-P75)*	68 (51.5-80.5)	67 (47.5-80)	>0.05
Body weight (gr) (P25-P75)	8100 (3850-12250)	7800 (3550-11850)	>0.05
Time of beginning complementary food (months)	5±1	5±1	>0.05
Feeding type			
- Breastmilk	26	14	>0.05
- Breastmilk + Formula	24	15	>0.05
- Formula	2	2	>0.05
Skin symptoms			
- Atopic dermatitis	47 (90.4%)	N/A**	
- Urticaria	5 (9.6%)	N/A**	
Time of appearance of skin findings (months)	5 (2-11)		
Gastrointestinal symptoms			
- Vomiting	N/A	13 (41.9%)	
- Rectal bleeding	N/A	18 (58.1%)	
Respiratory symptoms			
- Wheezing	5	4	
Median ECP (ng/ml) (P25-P75)	56.5 (4-220)	33.1 (14.4-56.8)	0.001
Median Eosinophil count (mm3) (P25-P75)	470 (30-1720)	270 (110-960)	0.006
Percentage of eosinophils	4.5 (0.4-18.3)	2.8 (1-9.6)	0.012

*P25-P75: Median values, **N/A: Not available.

Table-3: Correlation between ECP and eosinophil counts in the CMPA subgroups.

Parameters	Group with skin manifestations, n=52		Group without skin manifestations, n=31	
	r [a]	P- value	r [a]	P- value
Eosinophil counts	0.537	0.000	0.280	0.127

[a] Spearman's rank correlation.

4- DISCUSSION

In this study, we aimed to determine the frequency of skin manifestations in infants with CMPA in Karabük, Turkey. The most common clinical presentations of CMPA was skin lesions more commonly associated with atopic dermatitis, whereas symptoms related to gastrointestinal tract were the second most common Of 52 (62.6%) infants with CMPA gastrointestinal tract (GIT) involvement was detected as the second finding. The most commonly identified clinical finding in infants with CMPA at the time of the first presentation was related to the skin with a rate of 62.6% (most commonly AD), whereas findings related to GIT were the second most common. Besides, ECP, eosinophil count and eosinophil percentage were also found to be high in CMPA cases with AD detected. The prevalence of CMPA, which is the most common cause of food allergies and AD in the infant period, has increased in recent years (15, 16, 22). AD is the cutaneous manifestation of a systemic disorder related to an inflammatory disease of the skin with an itchy and chronic course mostly associated with allergic sensitization, most commonly observed in childhood (23, 24).

Although its etiology is not fully known, it has been reported that many factors occurring with the effects of environmental and infectious factors besides genetic factors play a role (25). Although AD can be observed in children with different ethnicities, the prevalence in Asian children has been reported to be higher than in other races. AD most frequently begins in the first 6 months of life although it can be seen in every age period. In addition, those with a family history of atopy may present earlier skin findings and AD is more commonly observed in boys than in girls (26-28). In 2010, Santos et al. from Portugal reported in their study in which they included 139 cases with CMPA in the first 2 years of age that 53% of the cases were male and that 35% had a history of atopy in their family (29). Also, the authors reported that in 51% of the cases multiple organs were involved, 73% of the cases had multiple findings, 81% had clinical symptoms related to skin, whereas 55% had GIT, and 16% had respiratory symptoms. In another study conducted by Suh et al. in 2011 with 115 cases with CMPA in the first 2 years of age, it was reported that 67% of the patients with CMPA who developed AD were male and 49.6% had a history of atopy in their family (30).

The median age of the infants in our study was 6 (1-12) months, and similar to previous studies, 55.4% (46) of the cases were male and 37.3% (31) had atopy history in their families. The frequency for clinical findings of GIT and respiratory system in cases in our study was also similar to data in the study by Santos et al. [56.6% (47) bloody diarrhea, 32.5% (27) vomiting, 10.8% (9) wheezing, respectively]; while the incidence of family history of atopy in cases with CMPA in the study by Santos et al. was similar to data in our study (37.3%), the incidence of skin findings was lower in our study (62.6%). The reason for this difference may be due to the diversity of

racial and genetic factors among study groups. Another reason may be that, in the studies by the above authors, the skin findings observed during the follow-up of infants diagnosed with CMPA were emphasized, while in this study skin involvement was considered as the first clinical presentation of the disease. During inflammation in the intestines, eosinopoiesis in the bone marrow increases with the effect of stimuli, releasing eosinophils into the circulation (31, 32). Eosinophils play a role in the cellular immune response triggered by cow's milk proteins by migrating to inflammatory foci and areas due to their pro-inflammatory and protective roles against exogenous pathogens to ensure homeostasis in the intestines (33-35).

The sECP level and eosinophil count may increase in the course of allergic inflammatory diseases such as CMPA. The sECP level and eosinophil count can be used as an indicator for acute exacerbation and follow-up of allergic diseases with inflammatory processes, such as AD, due to these properties of sECP, whose biochemical structure and function are the best known (36-38). Sugai et al. reported that the mean sECP level (21.2 ± 18.7μg/L) in AD patients was significantly higher than in the control group (5.8 ± 2.3μg/L) ($p<0.005$), and that there was a positive correlation between blood eosinophil count and the level of sECP ($r = 0.740$, $p<0.01$) (39). In another study, Li, Jingwen et al. reported that the blood eosinophil count (0.89 ± 0.45/mm^3) was significantly higher in young infants with a diagnosis of CMPA in the first 6 months compared to the control group (0.26 ± 0.12/mm^3) ($p<0.01$) (38). The median sECP level of the infants included in the study was 44 (4-220) ng/mL, and the median eosinophil count was 400 (30-1720)/mm^3. Consistent with previous studies, we found that the sECP and eosinophil levels of infants with skin findings were higher than those without skin involvement in this study (56.5 (4-220) ng/mL and 470 (30-1720)/mm^3, respectively, 33.1 (14.4-56.8) ng/mL and 270 (110-960)], ($p = 0.000$, $p = 0.006$, respectively), and a positive correlation was found between sECP level and eosinophil count ($r = 0.537$, $p = 0.000$). Our findings support the view that the eosinophil count and sECP level may increase in the course of allergic inflammatory diseases.

4-1. Study Limitations

There were some limitations in this study. First, the sample was small in the present study. Second, since this was a single-center study, the results cannot be generalized to the whole of Turkey.

5- CONCLUSION

In conclusion, our results demonstrate that AD in infants is common and is particularly associated with CMPA. Moreover, the CMPA infants with skin involvement had significantly higher sECP levels and eosinophil counts than CMPA infants without skin involvement. Therefore, pediatricians should be aware that AD may be the first clinical presentation of CMPA and not forget that the elimination diet has an important role in the treatment of both diseases.

6- CONFLICT OF INTEREST: None.

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