

The Relationship Between ABO and Rh Blood Types and Cow's Milk Protein Allergy

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ABSTRACT

Objective: Cow's milk protein allergy (CMPA) is the most common type of food allergy among infants. Several studies have found an association between ABO blood types and allergies such as allergic rhinitis, asthma, and atopic dermatitis, but the role of blood type differences in cases of IgE-mediated CMPA and food protein-induced-allergic proctocolitis (FPIAP) is not known yet.

Methods: A total of 100 patients born in our hospital approximately 2017-2021 and followed up in our Paediatric Allergy Clinic with the diagnosis of IgE-mediated CMPA and FPIAP, and as the control group, 259 children born in our hospital who had no family history of atopy and no signs of allergic disease in the follow-up were included in the study. Blood types of healthy children, and those with IgE-mediated CMPA and FPIAP diagnosis were compared.

Results: One hundred patients with CMPA were included in the study. The mean age of these patients was 10.8 months, and 49% (n=176) were male. 57% of the patients were followed up with a diagnosis of IgE-mediated CMPA and 43% with FPIAP. Familial atopy accompanied 23% (n=23) of the cases with CMPA. There was no statistically significant difference between the distribution of ABO and Rh blood types between the cases with CMPA and the control group ($p>0.05$). Additionally, there was no significant difference in blood type comparisons of the cases followed up with the diagnosis of IgE-mediated CMPA and FPIAP ($p>0.05$).

Conclusion: As far as we know, this is the first study of investigating the relationship between the blood type distribution of patients with CMPA and healthy subjects. To comprehend the role of blood type in the pathogenesis of CMPA and investigate the effect of blood types on tolerance development in CMPA cases, we think prospective studies with wider groups are necessary.

Keywords: Cow's milk protein allergy, ABO blood type, Rh blood type, tolerance

INTRODUCTION

Cow's milk protein allergy (CMPA) is the most common type of food allergy in infants.¹ CMPA occurs through three types of immune mechanisms. Immunoglobulin E (IgE)-mediated reactions are characterized by acute symptoms involving one or more target organs such as the skin, respiratory system, and gastrointestinal tract. The non-IgE-mediated form are late-onset reactions with clinical manifestations such as enterocolitis or proctocolitis. There

is also the "mixed type" in which both reactions are involved. This occurs with clinical findings such as atopic dermatitis and eosinophilic gastroenteropathy.¹⁻³

Food protein-induced-allergic proctocolitis (FPIAP) is one of the non-IgE-mediated food allergies.^{4,5} FPIAP is a disease characterized by immune response triggered by the intake of allergen food proteins from breast milk and inflammatory changes in the rectum and distal sigmoid colon.⁶ It is a benign disease that usually starts

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in the first months of life and characterized by bloody stools in well-appearing infants, and one of the major causes of colitis in infants younger than one year old.^{4,5,7}

The distribution of blood types can be affected by race, ethnicity, geographical conditions, and genetic reasons.⁸ Blood types play a role in immunity. Additionally, many relationships have been shown between cardiovascular diseases, cancers, and autoimmune diseases and blood types.^{9,10} There are few studies investigating the effect of blood types on allergic diseases. Data are unexpected, especially in the childhood age group. In a few studies conducted to date, allergic rhinitis is mostly associated with B and A blood types¹¹⁻¹⁴, asthma with O blood type¹⁵⁻¹⁸ and A blood type¹⁹, atopic dermatitis with O blood type.^{20,21} However, the role of blood type differences in IgE-mediated CMPA and FPIAP cases is not known yet.

There is no study in the literature investigating the distribution of blood types in patients with CMPA. In this study, it was aimed to investigate the relationship between ABO and Rh blood types and CMPA.

MATERIALS AND METHODS

Study Population

The study included 100 cases born in our hospital, followed up in our Paediatric Allergy Clinic with the diagnosis of IgE-mediated CMPA and FPIAP, and 259 healthy children, who were born in our hospital as the control group, with no family history of atopy and no signs of allergic disease in the follow-up. The clinical and laboratory results of the patients were recorded retrospectively from their file records. The presence of food sensitivity was evaluated with skin prick test and food-specific IgE (sIgE) test. In IgE-mediated CMPA cases, the diagnosis of cases without anaphylaxis was confirmed with an oral food challenge test (OFC).² The diagnosis of FPIAP was established in a patient who developed bloody stool after ingestion of suspicious food in accordance with the European Academy of Allergy and Clinical Immunology guideline, with the regression of his symptoms after the elimination diet and the recurrence of symptoms after the OFC test.⁴ ABO and Rh blood types of healthy children and blood types of patients with IgE-mediated CMPA and FPIAP were compared.

Patients with missing data in the file, patients whose diagnosis of CMPA could not be proven by performing an OFC test after elimination, infection leading to bloody diarrhea, anal fissure, perianal dermatitis/excoriations, intussusception, coagulation defects, necrotizing enterocolitis, inflammatory bowel disease, vitamin K deficiency, cases with diseases such as immunodeficiency, and cases with underlying chronic gastrointestinal system disease were excluded from the study. Informed consent was acquired from the parents of all patients who were then approved by the Research Ethics Committee of Istanbul Medipol University Hospital. Local ethics committee approval was obtained from Non-Invasive Clinical Research Ethics Committee of Istanbul Medipol University for the study (E-10840098-772.02-2630/21.01.2021, decision no: 84).

Evaluation of Laboratory Parameters

ABO and Rh Blood Types

Blood type typing was determined using the gel centrifugation method with the DiaClon ABO/Rh for New-borns DVI+ monoclonal Ab kit (Bio-Rad, Cressier, Switzerland).

Skin Prick Test

The skin prick test was performed on all patients with fresh food (one drop of each fresh milk containing 3.5% fat) and commercial extracts (ALK-Abello A/S, Horsholm, Denmark standard prick test, cow's milk). Histamine (10 mg/mL) was used as positive control and NaCl (0.9%) as negative control. The sensitivity of ≥ 3 mm compared to the negative control was considered allergen sensitivity.

Total IgE and Allergen-specific IgE Measurement

Total serum IgE, cow's milk sIgE measurement was done by ELISA method. Values above 0.35 kU/l were considered positive for sIgE.

Oral Food Challenge

The OFC was performed as an open challenge test after 2-4 weeks of elimination of the suspect food according to standard guidelines, except for children with a history of anaphylaxis.^{2,4} Patients who received only breast milk were evaluated by provoking the mother after elimination. In the presence of objective findings such as exacerbation of atopic dermatitis, urticaria, angioedema, signs of airway obstruction (dyspnoea, rhonchi, wheezing, etc.), vomiting and anaphylaxis during the food challenge test, the test was considered positive and terminated. The patient, who could consume all steps without developing a reaction, was considered negative in the OFC and was followed up for 5-7 days in terms of late reactions. For cow's milk allergy, OFC was started with 0.1 mL diluted using pasteurized cow's milk or formula, according to the age of the patient, and continued with increasing doses every 15-30 minutes until 200 mL milk was reached or a reaction was recorded. Patients who did not show a reaction in the food challenge test were followed up in terms of late reactions and their reaction status was recorded.^{2,4}

Statistical Analysis

The data were analysed using the SPSS 24.0 (Statistical Packages of Social Sciences) program on the computer. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test; continuous variables were shown as mean \pm standard deviation and median, and categorical variables as frequency and percentage. Since age, total IgE and percentage eosinophil variables did not fit the normal distribution, non-parametric test (Mann-Whitney U test) was used for comparison and median values were compared. Chi-square test was used for the statistics of the obtained data. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 100 with CMPA were included in the study. The mean age of the patients was 10.8 ± 10.21 months, and 49% (n=176) were male. 57% of the patients were followed up with IgE-mediated CMPA and 43% with FPIAP. There was a familial history of atopy in 23% (n=23) of the cases with CMPA. The most frequent symptoms were rash (51%, blood in stool (28%), cough (14%), and vomiting (10%).

No statistically significant difference was found between the gender distribution and mean age of the control group and the cases followed up with the diagnosis of CMPA ($p > 0.05$) (Table 1). The male sex ratio in IgE-mediated CMPA cases was found to be significantly higher than the group followed up with the diagnosis of FPIAP ($p = 0.03$) (Table 2). There was no statistically significant difference between the patients with CMPA and the control group in terms of the distribution of ABO and Rh blood types ($p > 0.05$). Additionally, there was no significant difference in blood type comparisons of the cases followed up with the diagnosis of IgE-mediated CMPA and FPIAP ($p > 0.05$) (Table 2). The comparison of age, total IgE and eosinophil percentage values of IgE-mediated CMPA and FPIAP cases are given in Table 2. Age at diagnosis was found to be significantly higher in IgE-mediated CMPA cases compared to FPIAP cases ($p < 0.001$) (Table 2). In the univariate logistic regression analysis, blood type distribution was not found to be a significant risk factor for the presence of CMPA (IgE-mediated CMPA and/or FPIAP) ($p > 0.05$) (Table 3).

DISCUSSION

In this study, in which the relationship between ABO and Rh blood types and CMPA was investigated, no significant difference was found between the blood types of the patients followed up with the diagnosis of CMPA and the blood types of healthy children. To date, blood types have been associated with many diseases such as cardiovascular diseases, cancers, autoimmune diseases, parasitic infections.²² Additionally, various studies have found a relationship between blood types and allergic diseases such as atopic dermatitis, asthma, and allergic rhinitis. Falsarella et al.¹¹, in their study investigating the relationship between ABO blood types and allergic rhinitis, reported that blood type O was associated with allergic rhinitis in men, but not in women. There are many studies supporting the relationship between allergic rhinitis and O blood type.¹²⁻¹⁴

Various results have been obtained in studies investigating the relationship between blood types and asthma. Kauffmann et al.¹⁵ and Ronchetti et al.¹⁶ showed that the frequency of asthma is higher in patients with non-secretory O blood type. Chen et al.¹⁷ reported that there is a relationship between asthma and blood types in patients with secretory O blood type. Manisha and Yadav¹⁸ showed a significant relationship in patients with O blood type, and Alo et al.¹⁹ stated that there was a relationship between A blood type and asthma. However, there are also studies stating that there is no statistically significant difference between asthma and blood types.^{23,24} In addition to asthma and allergic rhinitis, there are studies examining the relationship between atopic

Table 1. Distribution of gender and blood types according to patient and control groups, and comparison of mean/median age

	Patient (n=100)		Control (n=259)		Total	p*
	n	%	n	%	n	
Gender						0.484
Male	52	52.0	124	47.9	176	
Female	48	48.0	135	52.1	183	
Blood type						0.733
A	43	43.0	99	38.2	142	0.407
AB	7	7.0	26	10.0	33	0.372
B	13	13.0	38	14.7	51	0.684
O	37	37.0	96	37.1	133	0.991
Blood type						0.991
O	37	37.0	96	37.1	133	
Non-O	63	63.0	163	62.9	226	
Rh						0.634
Rh (-)	13	13.0	29	11.2	42	
Rh (+)	87	87.0	230	88.8	317	
	Mean±SD	Median [IQR]	Mean±SD	Median [IQR]		p**
Age (months)	10.89±10.4	9 [10]	10.76±10.17	9 [10]		0.939

*Chi-square test was used, **Mann-Whitney U test was used.

SD: Standard deviation, IQR: Interquartile range

Table 2. Gender and blood type distributions in the patient group according to the diagnosis types, and comparison of mean/median age, total IgE and % eosinophil values by diagnosis groups						
	IgE-mediated CMPA (n=57)		FPIAP (n=43)		Total	p*
	n	%	n	%	n	
Gender						0.03
Male	35	61.4	17	39.5	52	
Female	22	38.6	26	60.5	48	
Blood type						0.307
A	27	47.4	16	37.2	43	0.31
AB	2	3.5	5	11.6	7	0.115
B	6	10.5	7	16.3	13	0.397
O	22	38.6	15	34.9	37	0.703
Blood type						0.703
O	22	38.6	15	34.9	37	
Non-O	35	61.4	28	65.1	63	
Rh						0.723
Rh (-)	8	14.0	5	11.6	13	
Rh (+)	49	86.0	38	88.4	87	
	Mean±SD	Median [IQR]	Mean±SD	Median [IQR]		p**
Age (month)	14.61±13.45	10 [10]	5.83±3.6	5 [5]		<0.001
IgE total	243.22±252.74	139.25 [442.94]	15.19±21.3	10.63[13.64]		<0.001
% Eosinophil	4.61±3.02	4.4 [5.48]	5.15±4.16	3.9 [3.85]		0.745

*Chi-square test was used, **Mann-Whitney U test was used.
CMPA: Cow's milk protein allergy, FPIAP: Food protein-induced allergic proctocolitis, SD: Standard deviation, IQR: Interquartile range

Table 3. Logistic regression risk analyses according to blood types for the diagnosis of CMPA						
	CMPA (IgE-mediated and FPIAP cases)					
	B	SE	Wald	p	OR	Lower-Upper (%95 CI)
A	0.198	0.239	0.687	0.407	1.219	0.763-1.948
B	-0.14	0.345	0.165	0.684	0.869	0.442-1.71
AB	-0.394	0.443	0.79	0.374	0.675	0.283-1.608
O	-0.003	0.244	0	0.991	0.997	0.618-1.608
Rh (+)	0.17	0.357	0.227	0.634	0.844	0.419-1.698

Univariate logistic regression analysis was used.
CMPA: Cow's milk protein allergy, FPIAP: Food protein-induced allergic proctocolitis, OR: Odds ratio, CI: Confidence interval

dermatitis and atopic diseases and blood type. Gangopadhyay et al.²⁰ reported in their study that B blood type was the most common in patients with atopic dermatitis, followed by A blood type, and O blood type was detected less frequently in the atopic dermatitis group than in the control group. In another study, it was reported that the most common blood type in patients with atopic dermatitis was B blood type and it was associated with the development of allergy.²¹ Brachtel et al.²⁵ reported that blood types A and B are associated with atopic diseases such as rhinitis, asthma, and dermatitis.

In the study investigating the relationship between food allergies and blood types; Relationships have been reported between B and Rh negative blood types and IgE-mediated food allergies, and between O, A, and Rh negative blood types and IgG-mediated food allergies.²⁶

The prevalence of food allergy is higher in males.^{4,27} Studies conducted in England and China have also reported that the frequency of food allergies is higher in males.^{28,29} Similarly, Hikino et al.³⁰ also stated that male gender is a risk factor for food allergies and atopic dermatitis. Yavuz et al.³¹ reported in their

study that IgE-mediated food allergies are more common in males. Elizur et al.³² FPIAP, Katz et al.³³ stated that food protein-induced enterocolitis syndrome (FPIES) was more common in males. In our study, the ratio of males in the IgE-mediated group was found to be significantly higher than in the FPIAP group ($p=0.03$).

Study Limitations

We think that the limitation of our study is that the long-term prognosis is not followed to investigate the effect of blood types on the development of tolerance in patients with CMPA. As with other food allergies, several factors affect tolerance in CMPA. These; genetic predisposition, infections, changes in intestinal flora, age, frequency and amount of exposure, antigens passed through breast milk, mother's diet.³⁴ Since there are many factors affecting tolerance, we think that long-term studies are needed to investigate the tolerance relationship between blood types and CMPA.

CONCLUSION

In conclusion, to the best of our knowledge, this is the first study to investigate the relationship between the distribution of blood types in patients with CMPA and healthy subjects. To comprehend the role of blood type in the pathogenesis of CMPA and to investigate the effect of blood types on the development of tolerance in CMPA cases, we think that prospective studies with large groups are needed to evaluate clinical symptoms and more parameters.

Ethics

Ethics Committee Approval: Local ethics committee approval was obtained from Non-Invasive Clinical Research Ethics Committee of İstanbul Medipol University for the study (E-10840098-772.02-2630/21.01.2021, decision no: 84).

Informed Consent: Informed consent was acquired from the parents of all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.T., H.T.N., Concept: F.N.A., H.T., Design: F.N.A., H.T., H.T.N., Data Collection or Processing: F.N.A., H.T., Analysis or Interpretation: F.N.A., H.T., H.T.N., Literature Search: F.N.A., H.T., H.T.N., Writing: F.N.A., H.T., H.T.N.

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