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Evaluating the Role of Antibiotic Use in the Development of Cow's Milk Protein Allergy within the First Year of Life among the Patients Treated in the NICU

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Abstract

Background: It has been reported that the incidence of Cow's Milk Protein Allergy (CMPA) has increased in recent years, especially among infants in the first year of life. It is thought that the use of antibiotics may trigger the development of CMPA by causing intestinal dysbiosis and altering immune response, and thus, it may be a factor responsible for the supposed increase. The relationship between antibiotic use and the development of CMPA has been evaluated in very few studies in the literature. Thus, this study aimed to evaluate whether CMPA development is associated with antibiotic use during pregnancy or neonatal period.

Method: During the study period, 1120 babies were followed up in our NICU, 975 of whom met the inclusion criteria. The development of CMPA within the first year of life was evaluated among the infants hospitalized and followed up in the Neonatal Intensive Care Unit (NICU) of Karabuk University, Faculty of Medicine, Training and Research Hospital, between January 1, 2017 and October 30, 2020.

Results: The neonates whose mothers had used antibiotics received mechanical ventilation treatment at a significantly higher frequency ($p = 0.042$). There was no significant difference in the frequency of CMPA development between the infants of mothers with and without antibiotic use ($p = 0.533$). Compared to the babies who did not use antibiotics, the gestational week, birth weight, 1st and 5th minute APGAR scores of the babies who used antibiotics were significantly lower, and their frequency of mechanical ventilation treatment was significantly higher ($p<0.001$). There was no significant difference between infants who used and did not use antibiotics in terms of the frequency of CMPA development ($p = 0.150$). In general, it was found that the use of antenatal and postnatal antibiotics did not increase the development of CMPA.

Conclusion: The data of our study contradicts the two study of which previously associated maternal and infant antibiotic use with the development of CMPA. This contradiction suggests that the aetiology of CMPA is multifactorial and more studies are needed to elucidate the antibiotic-CMPA relationship.

Key Words: Antibiotic, Cow's milk protein allergy, Newborn.

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1- INTRODUCTION

Cow's milk protein allergy (CMPA) is the foremost cause of food allergy in the infancy. There is evidence that the incidence of CMPA has increased in recent years, especially within the first year of life. It has been reported that approximately 2–3.4% of infants develop symptoms related to CMPA during the first year after birth (1-2). The condition is defined as an immunological reaction to cow milk proteins accompanied by various signs and symptoms, the majority of which are gastrointestinal, but dermatological and respiratory symptoms may also occur (3-4).

In new-born babies, colonization of organs such as the intestines, skin and lungs after birth with appropriate bacteria is necessary for the maturation of the immune system. The formation of this colonization by unsuitable bacteria is defined as dysbiosis. Antibiotic use in new-born babies is the most common cause of dysbiosis (5). Additionally, healthy development of gut microbiota plays an important role in the development and maturation of the immune system and oral tolerance. Therefore, it is assumed that factors which disrupt the intestinal microbiota, such as antibiotics, may trigger the development of food allergies (30).

When the literature is examined, it is observed that allergic problems such as asthma and eczema are examined more frequently with respect to their relationships with antibiotic use in the new-born period and early infancy; however, studies focusing on the relationships between antibiotic use and development of CMPA or other food hypersensitivity problems are few (6-10).

Our primary aim is to evaluate whether taking antibiotics during hospitalization in our newborns in our neonatal intensive care unit is risky for the development of CMPA in the first year of life. In addition, our secondary aim was to evaluate the impact of their mothers' antibiotic use during pregnancy during pregnancy on the development of CMPA in the babies.

2- MATERIALS AND METHODS

This study was planned as a retrospective, cross-sectional study. The participants included the babies who had been hospitalized in the Neonatal Intensive Care Unit of Karabuk University, Medical Faculty Training and Research Hospital, between January 1, 2017 and October 30, 2020. All available data pertaining to the babies' first year of life were evaluated retrospectively from the hospital files. Babies discharged from the NICU are called to the neonatal outpatient clinic regularly once a month for the first 6 months, and once every 2 months between the ages of 6 months and 1 year. In these controls, milk and food allergy are questioned together with a general medical examination.

During the study period, 1120 babies were followed up in our NICU, 975 of whom met the inclusion criteria. The patients who were hospitalized in the Neonatal Intensive Care Unit were primarily divided into two groups, those who received antibiotics (group 1) and those who did not receive antibiotics (group 2). In addition, another grouping was also made based on maternal antibiotic use during pregnancy. It was questioned whether these babies, according to the records of the paediatric outpatient clinic, neonatal outpatient clinic and paediatric gastroenterology outpatient, developed CMPA in their first year. The weeks of gestation, mode of delivery, and whether the mother or baby used antibiotics were noted from the files of the patients.

The diagnosis of CMPA was made according to the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Guidelines (31). In most cases of suspected CMPA,

the definitive diagnosis needs to be confirmed or excluded by oral food challenge (OFC) testing, skin prick tests (SPT), and specific IgE measurements. In our study, OFC test was performed to confirm the diagnosis of CMPA. A drop of cow milk-based infant formula was dripped onto the perioral area and the lips of the infants, and they were observed to assess allergic reactions. The dose was gradually increased to 100 ml and administerations repeated at regular intervals of 15-30 minutes. Results were classified as OFC 'positive' or 'negative'. Babies with multiple food allergy diagnoses were excluded from the study.

2-1. Inclusion and Exclusion criteria

The patients who were hospitalized in the Neonatal Intensive Care Unit of the target hospital, during the study period, except those with major congenital anomalies, those with multiple food allergy diagnoses, those who did not attend regular follow-ups, and those who died during the study period were included in the study.

2-2. Statistical Analysis

To analyze the data obtained during the study, SPSS software (version 25, IBM, USA) was used. Nominal data were expressed by frequency and percentage and compared between groups via utilization of the appropriate chi-square tests. Continuous data were expressed as mean ± standard deviation (SD) or median and 1st-3rd quartiles (25%-75% percentile values). Conformity of continuous data to normal distribution was evaluated with the Shapiro-Wilk test. The Mann-Whitney U test was used for between-group comparison of data, since there were no comparison pairs in which both sets of data conformed to normal distribution. The *p*-value of <0.05 was accepted as the limit (threshold) of significance.

3- RESULTS

The number of infants followed in our NICU during the study period was 1120. Three babies had major congenital anomalies; 16 babies were died in the neonatal period. Among the remaining infants, 126 were excluded from the study because hospital records showed that they had not attended scheduled regular follow-ups. The data of the remaining 975 infants were analyzed.

The mean age of the mothers was 31.39 ± 5.88 years, and the mean week of gestation was 36.51 ± 2.94 months. CMPA was detected in 3.2% of the infants (**Table 1**).

From among the infants, 23% of those whose mothers used antibiotics and 16% of those whose mothers did not use antibiotics received mechanical ventilation therapy. The neonates whose mothers had used antibiotics received mechanical ventilation treatment at a significantly higher frequency (p = 0.042). There was no significant difference in the frequency of CMPA development between the infants of mothers with and without antibiotic use (p = 0.533) (**Table 2**).

Compared to the babies who did not use antibiotics, the gestational week, birth weight, 1st and 5th minute APGAR scores of the babies who used antibiotics were significantly lower, and their frequency of mechanical ventilation treatment was significantly higher (p<0.001). There was no significant difference between infants who used and did not use antibiotics in terms of the frequency of CMPA development (p = 0.150) (**Table 3**).

When CMPA development status was evaluated according to delivery type, CMPA developed in 3.3% of babies born with caesarean section (C/S) and in 2.7% of babies born with normal spontaneous vaginal delivery (NSVD). There was no significant difference between the delivery type groups in terms of CMPA development frequency (p = 0.836).

Table-1: Distribution of clinical features in the whole study group

Variables		value
Age (year)		31.39 ± 5.88
Gestational week		36.51 ± 2.94
Birth weight (gr)		2890.85 ± 756.46
APGAR scores	1st minute	7.74 ± 1.69
	5th minute	8.96 ± 1.28
Antibiotic use	No	844 (86.6%)
	Yes	131 (13.4%)
Type of delivery	C/S	747 (76.6%)
	NSVD	225 (23.1%)
	Vacuum/ forceps intervention	3 (0.3%)
Infant antibiotic use	No	470 (48.2%)
	Yes	505 (51.8%)
Infant mechanical ventilation	No	812 (83.3%)
	Yes	163 (16.7%)
CMPA	No	944 (96.8%)
	Yes	31 (3.2%)

Continuous numerical variables were summarized as mean ± standard deviation, and categorical variables were summarized as number (percentage)

Table-2: Distribution of clinical features by maternal antibiotic use

Variables	Maternal antibiotic use				p
	No		Yes		
	Mean ± SD	Median (25%-75%)	Mean ± SD	Median (25%-75%)	
Age (year)	31.39 ± 5.92	31 (27 - 36)	31.38 ± 5.67	32 (26 - 35)	0.961
Gestational week	36.55 ± 2.94	37 (35 - 39)	36.23 ± 2.98	37 (34 - 39)	0.224
Birth weight (gr)	2896.57 ± 746.41	2980 (2400 - 3445)	2854.03 ± 820.37	2830 (2270 - 3475)	0.276
APGAR scores					
1st minute	7.74 ± 1.68	8 (7 - 9)	7.78 ± 1.73	8 (7 - 9)	0.543
5th minute	8.97 ± 1.26	9 (9 - 10)	8.89 ± 1.39	9 (8 - 10)	0.621
Type of delivery					
C/S	651 (77.1%)		96 (73.3%)		0.460
NSVD	190 (22.5%)		35 (26.7%)		
Vacuum/forceps intervention	3 (0.4%)		0 (0%)		
Infant antibiotic use					
No	410 (48.6%)		60 (45.8%)		0.554
Yes	434 (51.4%)		71 (54.2%)		
Infant mechanical ventilation					
No	711 (84.2%)		101 (77.1%)		0.042
Yes	133 (15.8%)		30 (22.9%)		
CMPA					
No	816 (96.7%)		128 (97.7%)		0.533
Yes	28 (3.3%)		3 (2.3%)		

Continuous numerical variables are summarized with mean ± standard deviation and median (first quartile – third quartile), and categorical variables are summarized as number (percentage).

Table-3: Distribution of clinical features with respect to neonatal antibiotic use

Variables	Neonatal antibiotic use				p
	No		Yes		
	Mean ± SD	Median (25%-75%)	Mean ± SD	Median (25%-75%)	
Age (year)	31.74 ± 5.96	31 (27 - 36)	31.07 ± 5.79	31 (27 - 35)	0.109
Gestational Weak	37.47 ± 2.16	38 (36 - 39)	35.61 ± 3.27	36 (34 - 38)	<0.001
Birth weight (gr)	3122.67 ± 651.27	3170 (2650 - 3575)	2675.11 ± 783.85	2690 (2130 - 3210)	<0.001
APGAR scores					
1st minute	7.95 ± 1.47	9 (8 - 9)	7.55 ± 1.85	8 (7 - 9)	0.001
5th minute	9.18 ± 1.07	9 (9 - 10)	8.77 ± 1.42	9 (8 - 10)	<0.001
Type of delivery					
C/S	358 (76.2%)		389 (77%)		0.789
NSVD	110 (23.4%)		115 (22.8%)		
Vacuum/ forceps intervention	2 (0.4%)		1 (0.2%)		
Maternal antibiotic use					
No	410 (87.2%)		434 (85.9%)		0.554
Yes	60 (12.8%)		71 (14.1%)		
Infant mechanical ventilation					
No	447 (95.1%)		365 (72.3%)		<0.001
Yes	23 (4.9%)		140 (27.7%)		
CMPA					
No	459 (97.7%)		485 (96.0%)		0.150
Yes	11 (2.3%)		20 (4.0%)		

Continuous numerical variables are summarized with mean ± standard deviation and median (first quartile – third quartile), and categorical variables are summarized as number (percentage)

There was no significant difference in maternal age, gestational week, birth weight and APGAR scores between infants who had and had not developed CMPA during the follow-up (p >0.05 for all) (**Table 4**).

4- DISCUSSION

In the present retrospective, cross-sectional and observational study, we found that neither the antibiotics used by the mother during pregnancy nor the antibiotics used by the new-born pose a risk for the development of CMPA.

Although there are studies suggesting a relationship between antibiotic use during early life and asthma or other allergic diseases in the childhood (eczema, atopic dermatitis, hay fever, and allergic rhinitis) (13-23), yet there are studies which have shown no such relationship (24-29).

Studies examining the effects of maternal or infantile antibiotic use on food allergies

and specifically CMPA are very limited in the literature.

Table-4: Distribution of clinical features with respect to the presence and absence of CMPA

Variables	CMPA				p
	No (Absent)		Yes (Present)		
	Mean ± SD	Median (25%-75%)	Mean ± SD	Median (25%-75%)	
Mother's age (year)	31.4 ± 5.89	31 (27 - 36)	31.19 ± 5.9	30 (27 - 35)	0.819
Gestational week	36.54 ± 2.93	37 (35 - 39)	35.48 ± 3.14	36 (34 - 38)	0.061
Birth weight (gr)	2898.62 ± 757.09	2962.5 (2380 - 3450)	2654.52 ± 708.34	2730 (2000 - 3290)	0.080
APGAR scores					
1st minute	7.73 ± 1.7	8 (7 - 9)	8.03 ± 1.22	8 (7 - 9)	0.645
5 th minute	8.96 ± 1.29	9 (8 - 10)	9.03 ± 1.14	9 (9 - 10)	0.841

Continuous numerical variables are summarized as mean ± standard deviation and median (first quartile – third quartile)

Eggesbo et al. described that maternal use of antibiotics during pregnancy and use of antibiotics within the child's first 6 months of life did not increase the risk of developing egg allergy at his/her 3 years of age (11).

Although the exact causes of CMPA and other food allergies have not been fully elucidated, a combination of genetic and environmental factors is thought to be effective.

Metsälä et al., in a large population-based cohort study investigating the relationship between maternal and child antibiotic use and CMPA, compared 16,237 cases of CMPA with a matched control group, and found that both maternal antibiotic use during pregnancy and postnatal antibiotic use in the baby were associated with CMPA development (2).

Contrary to the study by Metsälä et al., we did not find a significant relationship between none of the maternal or infantile antibiotic uses, and the development of CMPA during the first year of life among the patients who had been previously admitted to the NICU. This discrepancy may arise for several reasons. We tried to ensure as much homogeneity between groups as possible by comparing babies who were hospitalized and followed up in the NICU; however, we could only partially achieve the homogeneity we wanted. There were no significant differences in terms of C/S delivery, gestational week, birth weight, and APGAR scores when the groups formed according to maternal antibiotic use were compared. On the other hand, when the groups formed according to neonatal antibiotic use were compared, we observed that the gestational week at birth, birth weight, and 1st and 5th minute APGAR scores were lower in those that had used antibiotics, although similar to the previous grouping results, there was no difference between C/S delivery frequency. Furthermore, the use of mechanical ventilation was significantly more frequent in subjects with maternal or infantile antibiotic use, compared to the respective corresponding groups.

In a study by Metsälä et al., it was reported that several specific and commonly used antibiotics were associated with an increased risk of CMPA, and concluded that the strongest association was with

third-generation cephalosporins. According to the antibiotic protocol applied in our NICU, penicillin & aminoglycoside combination is preferred, and 3rd generation cephalosporins are only utilized in the presence of central nervous system infection—due to the rapid development of resistance and increasing risk of fungal sepsis. Of our 505 antibiotic patients, only 12 received trhe 3rd generation cephalosporins, and CMPA developed in one of these infants. The fact that cephalosporins were hardly ever used during the course of our study may be a factor that caused the lack of significant relationship between the use of antibiotics and the development of CMPA.

The role of factors such as prematurity, short duration of breastfeeding and C/S delivery is not clear in the emergence of CMPA symptoms and signs. Monjaraz et al., in their study investigating the possible role of perinatal factors in the development of CMPA among 101 children with CMPA in Mexico, observed that maternal antibiotic use during pregnancy and short duration of postnatal breastfeeding were both factors that posed a risk for CMPA development; whereas, premature birth and C/S delivery were not found to cause the increased risk (12). In our study, C/S delivery and prematurity were not detected as risk factors. We could not compare the durations of exclusive breastfeeding in the postnatal period, as it was found that most parents could not recall this information during follow-up studies.

In line with the previous literature, CMPA developed in 3.2% of the infants included in our study within the first year.

4-1. Limitations of our study

The limitations of the study include the small number of cases due to its retrospective, cross-sectional and single-centre design, the inability to achieve a completely homogeneous distribution of the patients' characteristics within comparative groups, the lack of data on antibiotic use after the neonatal period, and the unknown duration of exclusive breastfeeding.

5- CONCLUSION

Our study revealed that maternal antibiotic use during pregnancy or neonatal antibiotic use did not increase the risk of developing CMPA during the first year of life in patients who had been admitted to the NICU after birth. While there are studies reporting a positive relationship between common childhood allergic diseases, such as asthma and atopic dermatitis, and antibiotic use, there are also studies reporting no such relationships. Similarly, the findings of our study are inconsistent with the data reported by Metsälä et al., who reported that the risk of developing CMPA increases with the use of antibiotics in the mother or baby, and also the study by Monjaraz, who found that the risk of developing CMPA increases with the use of antibiotics during pregnancy. These contradictions show that the possible relationships between CMPA and other childhood allergic diseases are multifactorial, and therefore, more studies are needed to elucidate the aetiology of CMPA.

6- ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of Karabuk University Faculty of Medicine with the date November 1, 2021 and decision number #730. The study was performed in accordance with the Declaration of Helsinki and good clinical practice guidelines.

7- CONFLICT OF INTEREST

None.

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