

The Relationship between Gastroesophageal Reflux Disease and Allergic Proctocolitis in 1-6-Month-Old Infants

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Abstract

Background: A number of researches have discussed the overlap of symptoms or the simultaneous occurrence of allergic proctocolitis due to consuming cow's milk allergy and gastroesophageal reflux in infants. The present study aimed to assess the relationship between gastroesophageal reflux disease and allergic proctocolitis (eosinophilic) in one- to six- month-old infants.

Methods: This case-control study was performed on one- to six-month-old infants referred to the Pediatric Gastroenterology Clinic for whom gastroesophageal reflux disease was diagnosed as the case group (n=95); and the same number of age-matched infants without gastrointestinal problems referred for periodic care were included as the controls. (n = 95). The diagnosis of allergic proctocolitis was made for subjects whose WBC and RBC were found to be higher than the normal range in their stool samples.

Results: The prevalence of allergic proctocolitis in the two groups with and without reflux was 36.8% and 5.3%, respectively, indicating a significant difference ($P < 0.001$). According to the multiple logistic regression model, the chance of developing allergic proctocolitis in the case group with gastroesophageal reflux was 12.2 times higher than the control group (OR = 12.2, $P < 0.001$). Boys were also 2.6 times more likely to be affected by proctocolitis than girls (OR = 2.6, $P = 0.025$).

Conclusion: Developing gastroesophageal reflux, especially in boys, will be associated with an increased risk of developing allergic proctocolitis.

Key Words: Allergic proctocolitis, Children, Infants, Reflux.

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1- INTRODUCTION

Gastroesophageal reflux is one of the most common and major problems in infants, especially under the age of one year, which results in growth retardation, irritability, recurrent vomiting, restlessness, apnea and sleep disorders (1). Additionally, pathological reflux, contrary to the physiological type, can cause side effects such as esophageal bleeding, ulcers on the surface of the esophageal mucosa, scarring, dysphagia, esophageal metaplasia, Barrett's esophagus, esophageal carcinoma and pneumonia and thus early diagnosis and treatment of affected infants is important (2, 3). Because clinical signs of gastroesophageal reflux may be seen in other childhood diseases, including infantile colic, pneumonia, respiratory allergies, and airway hypersensitivity, early, low-cost, and non-invasive diagnostic methods and facilities should be considered for disease management (4). Moreover, since various studies have shown a direct relationship between gastroesophageal reflux and the occurrence of many complications and diseases in infants, the use of its screening methods in infants for timely detection and treatment and prevention of complications seems necessary.

Milk allergy is an adverse immune reaction to one or more proteins in cow's milk. Allergy symptoms can appear quickly or start gradually. The first may include anaphylaxis, a potentially life-threatening illness that requires treatment with epinephrine, among other measures, but the second condition may last for hours to days, and its symptoms include atopic dermatitis, esophagitis, enteropathy involving the small intestine, and proctocolitis involving the rectum and colon (5, 6). The incidence of adverse reactions to dietary protein is vaguely defined in infants who are exclusively breastfed. Evidence suggests that approximately 0.5 to 1 percent of

exclusively breastfed infants have allergic reactions to proteins present in cow's milk and secreted into breast milk (7). Allergic reactions to cow's milk protein appear to be less common in infants fed by human milk than in those fed by cow's milk formula (8). This may be due to the relatively low protein levels of cow's milk secreted in breast milk, the immunomodulatory agents in breast milk, or the difference in normal microbes in the intestines of breastfed and formula-fed infants (9). The inflammatory reaction of the rectum and end of the large intestine (sigmoid colon) is called allergic proctocolitis (10).

Gastroesophageal reflux disease and cow's milk allergy (CMA) both often occur in the first year of life (11). The pathogenesis of these two conditions is complex and involves multiple mechanisms of nutrition, motility, immunology, and hypersensitivity (12). A number of researches have discussed the overlap of symptoms or the simultaneous occurrence of CMA and gastroesophageal reflux (13). However, differentiating between the two disorders is still challenging due to the similarity of symptoms and the lack of accurate and useful diagnostic tests. Because gastroesophageal reflux has a wide variety of causes that may be associated with one of the different forms of allergy, specifically allergic proctocolitis, it is now hypothesized that removing protein from the diet of mother and infant is a step towards the treatment and improvement of gastroesophageal reflux disease in infants. The present study aimed to assess the relationship between gastroesophageal reflux disease and allergic proctocolitis (eosinophilic) in one- to six-month-old infants.

2- MATERIALS AND METHODS

This case-control study was performed on 1-6-month-old infants referred to the Pediatric Gastroenterology Clinic for whom gastroesophageal reflux

disease was diagnosed (as the case group); and age-matched infants without gastrointestinal problems referred for periodic care were included as the controls. All cases used breast milk or standard formula, and all mothers signed a written consent before entering the study. Existence of concomitant underlying diseases that predispose a person to reflux, such as structural and anatomical disorders as well as failure to follow instructions and perform tests were considered as the exclusion criteria. All subjects were studied to evaluate the association between gastroesophageal reflux and allergic proctocolitis.

First, the purpose of the study and the stages of the study were fully explained to the parents of the patients diagnosed with gastroesophageal reflux. Then, the patients who had the inclusion criteria such as consumption of breast milk or standard formula, aged 1-6 months, and their parents had full consent to enter the study were included in the sample. The parents were instructed to take a stool test (S/E) three times in three days and refer to the test results for follow-up. The control group consisted of one- to six-month-old infants presented for periodic care without any gastrointestinal problems. For this group, the S/E test was performed three times in three days. WBC and RBC stool counts for both case and control groups were carefully evaluated in the laboratory. Also, all subjects completed a checklist containing demographic information such as age and sex of the infant, and the parents were asked about their family history of allergies. Finally, the diagnosis of allergic proctocolitis was made for people whose WBC and RBC were found to be higher than the normal range in their stool samples. Then, by comparing the results obtained for the case and control groups, the relationship between gastroesophageal reflux and allergic proctocolitis was investigated.

2-1. Data analysis

Frequency and percentage were used to describe the qualitative variables and mean \pm standard deviation for quantitative variables. To examine the differences between the groups, Fisher's exact test or chi-square test was used for qualitative variables; independent t-test was used for quantitative variables with normal distribution and Mann-Whitney test for quantitative variables with non-normal distribution. Logistic regression model was used to obtain the odds ratio and its confidence interval for allergic proctocolitis. The analysis was performed by SPSS software and a significance level of 0.05 was considered in all tests.

3- RESULTS

A total of 190 infants participated in this study and were categorized in two groups of cases ($n = 95$) and controls ($n = 95$) with and without gastroesophageal reflux disease. The age of infants ranged from 12 to 285 days with a mean of 70.5 ± 44.6 days. Only 3 cases (1.6%) of infants were older than 180 days (6 months). As summarized in **Table 1**, the two groups were similar in terms of infant age, gestational age and family history of gastroesophageal reflux and did not differ significantly; however, boys were more likely to be in the gastroesophageal reflux group (57.9% versus 48.4%, $P = 0.025$) and Breast milk consumption was much lower in the patient group than in the control group (70.5% versus 84.2%, $P = 0.017$).

The prevalence of allergic proctocolitis in the two groups with and without reflux was 36.8% and 5.3%, respectively indicating a significant difference ($P < 0.001$). Regarding the prevalence rate of allergic proctocolitis according to the baseline characteristics (**Table 2**), the frequency of positive results for proctocolitis was higher in boys than girls (27.7% versus 13.5%, $P = 0.016$), but was

independent to other baseline variables including type of milk consumed, gestational age and family history of the disease.

According to the multiple logistic regression modeling (**Table 3**), the chance of developing allergic proctocolitis in the

case group with gastroesophageal reflux was 12.2 times higher than the control group (OR = 12.2, 95%CI: 4.3 to 34.3, P < 0.001). Boys were also 2.6 times more likely to be affected by proctocolitis than girls (OR = 2.6, 95%CI: 1.1 to 5.9, P = 0.025).

Table-1: Baseline characteristics of the participants

Characteristics		With reflux	Without reflux	P-value
Male gender (%)		55 (57.9)	46 (48.4)	0.025
Mean age (day)		62.4 ± 42.5	78.7 ± 45.4	0.927
Type of milk used	Breast milk	67 (70.5)	80 (84.2)	0.017
	Formula	1 (1.1)	2 (2.1)	
	Both	27 (28.4)	13 (13.7)	
Gestational age	Term	94 (98.9)	93 (97.9)	0.998
	Preterm	1 (1.1)	2 (2.1)	
Positive family history (%)		25 (26.3)	11 (11.6)	0.713

Table-2: The rate of Allergic proctocolitis according to baseline variables

Characteristics		With proctocolitis	Without proctocolitis	P-value
Gender	Male	12 (13.5)	77 (86.5)	0.016
	Female	28 (27.7)	73 (72.3)	
Type of milk used	Breast milk	34 (23.1)	113 (76.9)	0.45
	Formula	0 (0.0)	3 (100)	
	Both	6 (15.0)	34 (85.0)	
Gestational age	Term	39 (20.9)	148 (79.1)	0.51
	Preterm	1 (33.3)	2 (66.7)	
Family history (%)	Positive	30 (19.5)	124 (80.5)	0.27
	Negative	10 (27.8)	26 (72.2)	

Table-3: Results of logistic regression model of allergic proctocolitis according to the studied variables

Characteristics	Odds Ratio	95% Confidence Interval	P-value
Gastroesophageal reflux	12.2	4.3 – 34.3	< 0.001
Male gender	2.6	1.1 – 5.9	0.025
Age	1.0	0.99 – 1.009	0.922
Family history	1.2	0.46 -13.3	0.135
Type of milk used	0.5	0.31 – 0.89	0.017

4- DISCUSSION

Previous studies have reported gastric reflux overlap and esophageal allergy in 56-6% of infants with persistent

gastrointestinal symptoms and suspected reflux, regardless of breastfeeding or formula (14-16). Some of these studies have even shown that by eliminating cow's

milk products from the diet, the symptoms of gastroesophageal reflux group completely disappear, which confirms the causal relationship between the two conditions (17). In this regard, it has been reported that the evaluation of infants with cow's milk allergy is necessary for the presence of gastroesophageal reflux; Because with the treatment of cow's milk allergy through an elimination diet, reflux can also be controlled, which indicates the relationship between these two conditions and also prevents costly anti-reflux and additional treatments in these patients (18).

One of the most common and basic problems of infants, especially under the age of one year, is gastroesophageal reflux, which is observed in approximately 50% of infants under 2 months and 60-70% of infants with 3 to 4 months of age (19). Gastroesophageal sequelae in these infants include growth retardation, irritability, recurrent vomiting, restlessness, apnea, and sleep disturbances; and thus by timely diagnosis and finding the underlying causes of gastroesophageal reflux and elimination of the causative factors, a large number of problems in infancy can be solved (14).

Some studies have suggested an association between gastroesophageal reflux and milk allergy, so that the prevalence of milk allergy in children and infants with gastroesophageal reflux has been reported in the range of 16 to 59% (16, 20, 21). An allergy to animal proteins found in milk compounds can lead to inflammation of the gastrointestinal tract and manifest as allergic gastroenteritis, proctocolitis, or enterocolitis. Allergic proctocolitis is one of the causes of rectal bleeding in infants aged 1 to 6 months, which often occurs due to an adverse immune response to one or more cow's milk proteins in the mother's diet (22). Diagnosis of allergic proctocolitis is based on clinical features and improvement of the disease after changing the mother's diet

(21). Anal bleeding generally resolves within 96-72 hours after avoiding cow's milk protein. However, in about 7% of cases the hydrolyzed formula (eHF) should be used and in 5% the amino acid-based formula (AAF) should be used (23). Serum specific IgE is usually negative because IgE-mediated pathogenetic mechanisms are thought to be involved (22). Due to the lack of studies on the relationship between gastroesophageal reflux group and allergic proctocolitis in infants, the present study was performed to determine the association between gastroesophageal reflux with allergic proctocolitis (eosinophilic) in infants one to six months old.

There was a significant difference between the two groups with and without reflux in terms of sex distribution, so that 55% of the infants in the case group and 46% of the infants in the control group were male. However, there was no significant difference between the two groups with and without reflux in terms of mean age. In a study by Karimi et al. (24), on infants with reflux disease, the incidence of the disease was higher in boys. In a study by Farahmand et al. (23), 52% of infants with reflux were male. Another Epidemiological study also showed that gastric reflux occurs in approximately 50% of infants under 2 months, 60-70% of infants 3-4 months, and 5% of infants up to 12 months (25).

In the present study, the type of milk consumed in 67% of the case group (with reflux) was breast milk, 1% used powdered milk and 27% both; but in the control group 80% used breast milk, 2% powdered milk and 13.7% both. In addition, the family history of gastroesophageal reflux group in the case group with 26.3% was higher than the control group with 11.6%, although the two groups were not statistically significant in this regard. Other studies have reported that the frequency of

gastroesophageal reflux group in infants who are breastfed is lower than that in infants who are breastfed (25). Breastfeeding is associated with faster elimination of gastric reflux, because it is eliminated from the stomach much faster (19). A cohort study by Curien-Chotard et al. in 2020 (26), also reported two identified risk factors for neonatal reflux with a family history and inactive smoking exposure.

In the present study, the frequency of allergic proctocolitis in the two groups with and without reflux was 36.8% and 5.3%, respectively, which was statistically significant. With constant values of other variables in the logistic regression model, the chance of developing allergic proctocolitis in the case group was 12.2 times higher than the control group. The prevalence of cow's milk allergy in children with gastroesophageal reflux has been evaluated in a number of studies to date, however, no study has been found that exclusively examines the prevalence of allergic proctocolitis in these children. In a study by Moghtadari et al. (27) which assessed the prevalence of cow's milk allergy in children (mean age 2.9 years) with reflux and healthy children, the prevalence of cow's milk allergy (at least in one of Perrick's skin tests) Immunoglobulin E level and atopic patch test in the reflux group was significantly higher than the control group and the chance of developing cow's milk allergy was higher in the case group than the control group (odds ratio 1.78). In a study by Yukselen et al. (20) on 151 children (3 to 60 months) with refractory reflux, 58 (38.4%) had a positive oral milk challenge. In a study by Farahmand et al. (23), cow milk allergy was reported in 27 of 72 infants with gastroesophageal reflux group (37%) using the elimination of cow's milk from the diet. Overall, milk allergy has been reported in children and infants with gastroesophageal reflux group in the range

of 16 to 59%, due to differences in the studied populations (gastroesophageal reflux group or gastroesophageal reflux group-resistant gastroesophageal reflux group), study design, follow-up, and methods of diagnosing allergies (Skin testing, oral challenge, elimination of cow's milk from the diet, etc.). In general, the results of the above studies on the high prevalence of milk allergy in gastroesophageal reflux group infants are consistent with the present study and confirm the association of allergic proctocolitis with gastroesophageal reflux group. Regarding the mechanism of this association, it has been reported that in children with cow's milk allergy, the neuro-immune interactions resulting from the cow's milk challenge may cause gastrointestinal motility disorders, which in turn increases the number of reflux cycles (14). Therefore, it is recommended that the infants with gastroesophageal reflux disease be evaluated for sensitivity to cow's milk and allergic proctocolitis. In infants with a positive result, necessary recommendations such as eliminating milk from the mother's diet and using powdered milk based on hydrolyzed proteins or based on amino acids should be provided to improve gastroesophageal reflux without drug treatment. In this regard, studies have shown that in children with sensitivity to cow's milk protein and gastroesophageal reflux, after 24 hours of diet without cow's milk, the symptoms of reflux have significantly improved in patients (14).

In the present study, although the prevalence of allergic proctocolitis in infants with a family history (27.8%) was higher than in those without a family history of allergies (19%), no significant difference was observed in this regard. In a study by Farahmand et al. (23), out of 27 infants diagnosed with reflux allergy, the family had a history of allergies in at least one parent (44.4%). In a study by Sardecka

et al. (28), on 118 healthy infants and 118 infants with bovine allergies, it was reported that a positive family history of allergies increased the risk of bovine allergies in the first year of life. However, in the study of Cavataio et al. (16), there was no difference in the clinical or family history between the patients with gastroesophageal reflux group and patients with gastroesophageal reflux group + CMPA.

One of the strengths of the present study was its case-control design that made it possible to evaluate allergic proctocolitis in children with gastroesophageal reflux group compared to healthy children. One of the limitations of the present study is the diagnosis of allergic proctocolitis based solely on fecal examination and clinical signs. It is recommended that other tests such as oral challenge or elimination from the diet be used in future studies to diagnose the allergic perch. In addition, it is recommended that the effectiveness of eliminating cow's milk from the mother's diet be investigated in the improvement of symptoms.

5- CONCLUSION

In the present study, the frequency of allergic proctocolitis in infants with gastroesophageal reflux group was 36.8%, which was significantly higher than that in the group of infants without gastroesophageal reflux (5.3%), and the chance of developing allergic proctocolitis in infants with gastroesophageal reflux group was 12.2 times higher than that in the healthy infants. Also, the frequency of allergic proctocolitis was significantly different according to gender; and the chance of developing allergic proctocolitis in boys was 2.6 times higher than girls. Therefore, developing gastroesophageal reflux, especially in boys, will be associated with an increased risk of developing allergic proctocolitis.

6- ETHICAL APPROVAL:

The study protocol was approved by the ethics committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1399.181).

7- ACKNOWLEDGEMENTS

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8- CONFLICT OF INTEREST

None.

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