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ORIGINAL PAPER

Can fecal calprotectin be a marker of allergic enterocolitis in infants and young children?

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ABSTRACT

Aim of the study: Aim of this study was to evaluate whether fecal calprotectin (FC) can be used as non-invasive biomarker of allergic enterocolitis and be helpful in differentiating with other inflammatory gastrointestinal conditions.

Material and methods: The retrospective study was performed on the group of 48 children, aged 1–36 months (mean 9.0 ±6.6) admitted to our Department for diagnostics of complaints from gastrointestinal tract. The inclusion criteria to analysis was the increased FC concentration (> 150 μg/g of stool) evaluated using ELISA method. Subjects were reviewed for the diagnosis, gastrointestinal symptoms, infectious parameters and allergic tests. The study group was then divided into three subgroups considering the cause of the increased FC concentration including 17 children with food allergy, 10 with infection and 14 with both of them. Seven children were excluded from the study due to the other diagnosis; 18 healthy, age comparable children, were qualified to the reference group.

Results: FC concentration was significantly higher in the group of children with allergy (mean 892.3 ±791.4 μg/g, $p < 0.001$), infection (mean 742.2 ±900.7 μg/g, $p = 0.046$) and both diagnosis (mean 1088.7 ±528.3 μg/g, $p < 0.001$) in comparison to the reference group (mean 81.5 ±37.3 μg/g), but no significant statistical differences were found between subgroups regarding to the cause of gut inflammation ($p > 0.05$). The main cause of infection was Staphylococcus aureus (50.0%); of allergy – cow's milk. The concentration of C-reactive protein was higher in the group of children with infection compared to allergic patients (14.3 ±32.5 mg/l vs. 3.1 ±3.7 mg/l; $p = 0.305$).

Conclusions: Food allergy as well as infection can be a cause of increased FC concentration. FC might only be useful as a screening test of allergic enterocolitis in infants and young children.

KEY WORDS:

infants, calprotectin, allergic colitis.

INTRODUCTION

Fecal calprotectin (FC) is a calcium- and zinc-binding, cytosolic protein, secreted extracellularly into the intestinal lumen, from stimulated neutrophils, eosinophils and monocytes [1]. The biochemical properties of FC as a high heat resistance and structure stability allow to eliminate it in an intact form in the feces and its concentration in stool correlates with the severity of gut inflammation [2].

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Actually, FC is used as a non-invasive biomarker for the diagnosis and monitoring of inflammatory bowel disease (IBD) in children and adults, being a guick and reproducible tool that facilitates the differentation of patients with organic gastrointestinal (GI) disease from those with functional disorders [3, 4]. It is known that FC concentration can also be increased in other organic and inflammatory diseases as: celiac disease, cystic fibrosis, juvenile idiopathic arthritis, connective tissue diseases, necrotizing enterocolitis and even infectious colitis of various etiology [5, 6].

Allergic enterocolitis is a common gastrointestinal manifestation of food allergy in infancy and early childhood associated with rectal bleeding, vomiting, diarrhea and impairment of growth. In most infants the hyperreactivity of immune system to food proteins, especially cow's milk proteins, leads to non-IgE-dependent gut inflammation. The results of skin prick tests or assessment of specific IgE antibodies do not determine the diagnosis and the only diagnostic tool by choice is an elimination diet followed by oral food challenge [7–9]. Therefore that the increased concentration of FC indicates the gut inflammation, we were interested if FC can be used as non-invasive biomarker of allergic enterocolitis and be helpful in differentiating with other inflammatory gut conditions in infants and young children.

Only few, currently published, studies have evaluated usefulness of FC in children with other than IBD conditions. Otherwise, most researches had a variety of limitations, including wide age range, small sample sizes and undefined reference range of FC for healthy children [2].

MATERIAL AND METHODS

Fourty eight children up to 3 years of age, preselected from the patients, admitted in 2016–2017 to our Department for diagnostics with symptoms from gastrointestinal tract, such as diarrhea, vomiting, bloody stools, failure to thrive, irritability, were enrolled to the retrospective study. The inclusion criteria to analysis was the increased FC concentration > 150 μg/g of stool determined using a commercially available enzyme-linked immunosorbent assay (ELISA) method as previously described [10] and the age 1–36 months. Calprotectin level was expressed as μg/g of feces. The measurement of calprotectin concentration was always carried out before the implementation of dietary and pharmacological treatment.

Among the selected subjects, we excluded *a priori* the patients aged less than 1 month and with the concomitant diseases as celiac disease, autoimmune disorders, cystic fibrosis and acute respiratory or urinary tract infection and being under the treatment with steroidal or non-steroidal anti-inflammatory drugs, proton pump inhibitors, antibiotics and probiotics two weeks before and during hospitalization, beacuse of a possible influence of these conditions on FC concentration. All subjects with the increased FC concentration were reviewed by medical documentation for the diagnosis, gastrointestinal symptoms, co-morbidities, family history, anthropometric and infectious parameters, results of occult blood test, stool culture and allergic tests.

Besides the clinical symptoms, the criteria for identifying the GI tract infection were: increased concentration of C-reactive protein, leukocytosis, stool culture indicating the presence of pathogenic flora and positive test for detection of rota/noro/adenovirus.

Lactose intolerance has been diagnosed primarily upon clinical symptoms and additionally, the result of Stool Reducing Substances Test. The diagnosis of IgE-mediated food allergy was based on the history of patients who experienced the reaction following ingestion of a specific food and on the increased concentration of serum food-specific IgE antibodies to main food allergens measured with a fluoroimmunoenzymatic essay (PolyCheck) according to the manufacture's instruction. Measurable specific IgE was defined as a positive test result if > 0.7 kU/l (2^{nd} class).

Patients with suspicion of non-IgE-mediated cow's milk protein (CMP) sensitization were underwent food elimination diet without cow's milk and its derivatives. The disappearance of symptoms was considered as a positive result and indicative of milk allergy. Non-IgE-mediated sensitization to other than milk allergens (egg white, soy, wheat) was verified also by the resolution of symptoms on the elimination diet. Eighteen healthy, age comparable individuals, from the same study period and with concentration of FC ≤ 150 μg/g of stool, were qualified to the reference group.

Statistical analysis was performed by using SPSS for Windows software (version 13.1; PL). The comparison of quantitative variables was carried out using the Student's t-test in case of normally distributed data and the Mann-Whitney test in case of nonparametric data. A *p value* <0.05 was considered statistically significant.

The research was conducted according to the principles of the Declaration of Helsinki and the local Ethics Committee approved this study (R-I-002/106/2017).

RESULTS

25 girls and 23 boys, aged 1–36 months (mean 9.0 ±6.6) were initially included in the retrospective analysis. 7 children were excluded from the study due to the different reasons: co-morbidities as anemia, congenital defect of the bile ducts, hipertransaminasemia, celiac disease and medical treatment.

Based on the data collected in individual's medical documentation, 41 children fulfilling the inclusion and exclusion criteria, were considered for the final analysis and divided into three groups considering the main diagnosis and cause of the increased FC concentration: group 1 – 17 children with food allergy (FA), group 2 –

10 with infection (I) and group 3 – 14 with both of them (FA/I) (Fig. 1). The total frequency of food allergy and GI tract infection among patients with increased FC was 31 (75.6%) and 24 (58.5%) children, respectively.

The groups were comparable with regarding to age, sex, family history of atopy. Atopic dermatitis was the most common disease in the families of children, according to the family history of atopy and was reported only in the group of patients with food allergy. Celiac disease was presented in the first degree relatives, only in the infection group (Table 1). Other clinical features as co-morbidities, clinical symptoms, physical examination findings, body mass index (BMI) were analyzed based on the patient's documentation and no statistically significant differences were found between the three groups. Analysis of the clinical status revealed, that in all investigated children concomitant disorders were reported: most of them had atopic dermatitis and lactose intolerance, but also no statisticaly significant differences were noted between groups (Table 1).

We compared the median FC concentrations in the groups and the results were as follows: in group 1 (FA): 892.3 µg/g ±645.6 (range: 193.1–2493.3 µg/g), in group 2 (I): 742.2 µg/g ±854.4 (range:197.7–3093.2), in group 3 (FA/I): 1088.7 µg/g ±627.3 (range: 351.5–2525.5); the values were significantly higher in all investigated groups in comparison to the control group: 81.5 µg/g ±36.25 (range: 21.9–142.2), but without statistically significant differences regardless to the cause of gut inflammation ($p > 0.05$). Detailed results are presented in Figure 2 and Table 2.

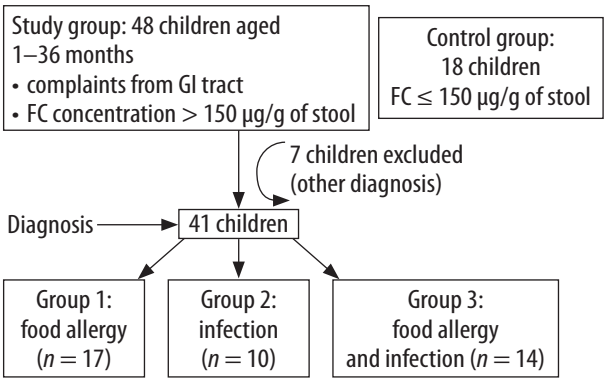

FIGURE 1. Study design

We also assessed potential differences between the mean concentration of C-reactive protein in each of the groups and we have shown that the values were higher in the group of children with infection in comparison to that one with allergy (14.3 ±32.5 vs. 3.1 ±3.7; $p = 0.305$) and both of them (14.3 ±32.5 vs. 7.3 ±16.7; $p = 0.203$), but these differences were not statistically significant.

The mean values of leukocytosis, hemoglobin and positive results of blood occult test were comparable between the three groups (Table 3).

The main causes of infection were *Staphylococcus aureus* ($n = 12$; 50.0%) and *Klebsiella oxytocyta* ($n = 4$; 16.7%) (Fig. 3).

The analysis of the results of specific IgE to the main food allergens, has shown, that 4 (12.9%) children have been diagnosed with IgE-depedent food allergy and three of them had sensitization to more than one food

TABLE 1. Main clinical features in the investigated groups of children

Clinical features	Group 1 ($n = 17$)	Group 2 ($n = 10$)	Group 3 ($n = 14$)
Age (in months), mean ±SD	10.1 ±6.2	11.1 ±8.8	6.3 ±4.5
Sex, *n* (%):			
boys	9 (52.9)	6 (60)	8 (57.1)
girls	8 (47.1)	4 (40)	6 (42.9)
Family history (n, %):			
allergy	2 (11.8)	0 (0)	0 (0)
celiac disease	0 (0)	1 (10)	0 (0)
Co-morbidities *(n*, %):			
lactose intolerance	6 (35.3)	4 (40)	7 (50)
atopic dermatitis	5 (29.4)	2 (20)	3 (21.4)
recurrent respiratory infections	3 (17.6)	0 (0)	0 (0.0)
Main symptoms (*n*, %):			
blood in the stool	9 (52.9)	5 (50)	12 (85.7)
diarrhea	8 (47.1)	5 (50)	9 (64.3)
feeding difficulties	4 (23.5)	3 (30)	2 (14.3)
BMI (kg/m^2)	14.6 ±1.9	16,6 ±5.7	16.2 ±3.2

*group 1 – food allergy, group 2 – infection, group 3 – food allergy and infection, *p-value: group 1 vs. 2 vs. 3 and group 2 vs. 3 – not statistically significant*

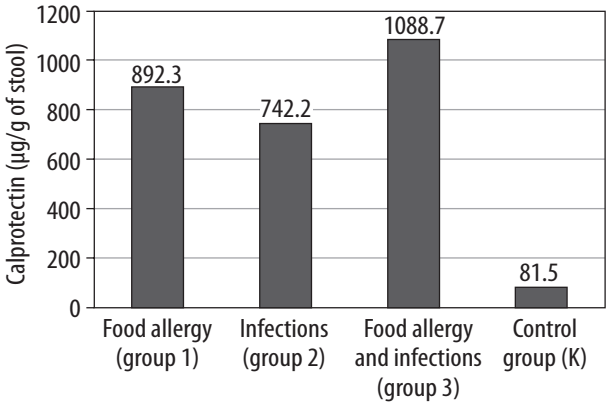

FIGURE 2. Fecal calprotectin concentration in the investigated groups and control subjects

allergen. The patients were predominantigly sensitized to cow's milk (n = 4; 12.9%); egg white (n = 2; 6.5%), codfish (n = 1; 3.2%). The FC concentration was comparable in patients with IgE-mediated food allergy to those with non-IgE-mediated (1210 ±987.6 µg/g vs. 1077 ±909.7 µg/g; p = 0.465). In 17 (54.8%) patients with IgE-mediated and suspicion of non-IgE-mediated milk allergy the disappearance of symptoms was observed after implementation of dairy-free diet. The mean time of resolution of symptoms was 4.2 ±1.1 days.

DISCUSSION

Allergic enterocolitis is a clinical diagnosis based on signs and symptoms from GI tract, the clinical improvement after initiation of the elimination diet and recurrence of symptoms after reintroduction of harmful food allergens. This non-IgE-mediated disorder affects about 2–3% of infants and the most severe form of disease is food protein-induced enterocolitis syndrome (FPIES); the mildest – food protein-induced allergic proctocolitis (FPIAP) [7–9].

Allergic enterocolitis has non-IgE-mediated immunological background and is actually diagnosed exclusively on the basis of clinical findings. Because the assesment of

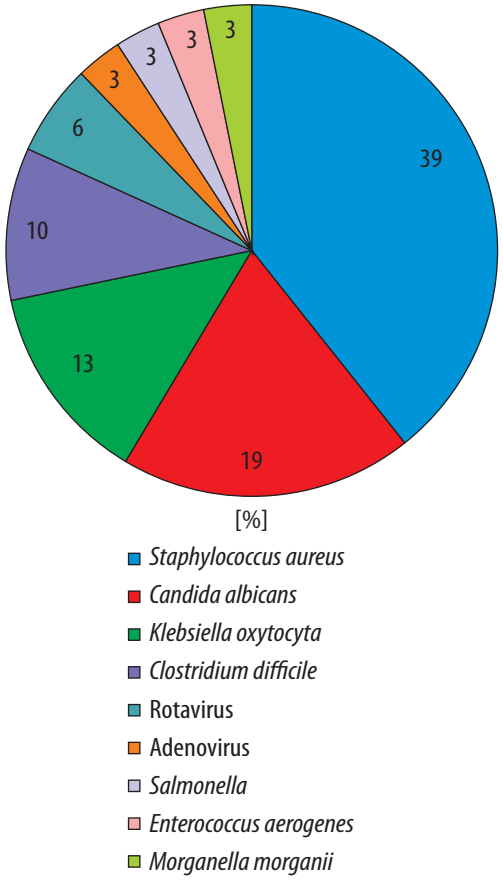

FIGURE 3. Stool culture in children with gastrointestinal tract infection

specific IgE antibodies or skin prick tests are lacking [8], we were interested about the usefulness of FC as a simple, non-invasive test that could be helpful in diagnosis of allergic enetrocolitis and in taking the decision of dietary intervention.

In the presented study, a reference calprotectin value of 150 µg/g in stool was used as a cut-off level, but there are conflicting data concerning appropriate reference values of FC in children [2]. The study population included almost 300 healthy children up to 18 months of age performed by Li *et al.* indicated that median FC concentra-

TABLE 2. Comparison of mean fecal calprotectin values between analysed groups vs. control

Value	Group 1 vs. control	Group 2 vs. control	Group 3 vs. control	Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
p	< 0.001	0.046	< 0.001	NS	NS	NS

NS – not significant

TABLE 3. Comparison of the main laboratory parameters between groups

Parameters	Group 1 (n = 17)	Group 2 (n = 10)	Group 3 (n = 14)
C-reactive protein (mg/l)	3.1 ±3.7	14.3 ±32.5	7.3 ±16.7
WBC (G/l)	11.8 ±4.5	11.2 ±2.4	13.8 ±4.1
Hb (g/dl)	11.6 ±1.3	11.3 ±1.8	11.4 ±1.2
Positive blood occult test (n [%])	6 (35.3)	2 (20.0)	9 (64.3)

WBC – white blood cells, Hb – hemoglobin, p-value: group 1 vs. 2 vs. 3 and group 2 vs. 3 – not statistically significant

tion showed a significant and negative correlation with age and achieve value of 375.2 μg/g in 1–3 months aged infants with decreasing to 104.2 μg/g in children aged 12–18 months [2].

Although reference values for FC in children have not been defined, all investigators admitted that there are higher than the normal levels in healthy adults. Sykora *et al*. suggested that still furher studies investigating FC reference ranges are required, especially in subjects younger than 12 months of age [11]. Children aged up to 3 years have higher concentration of calprotectin than adults, but there was no significant difference in FC between older children and adults. Interestingly, the calprotectin assay had a higher sensitivity and specificity in children than in adults, beacuse of the lower frequency of associated disease and use of drugs damaging the intestinal mucosa [3, 12].

In our study, higher values of FC have been found in infants with allergy as like with infection, but the differences were not statistically significant. Furthermore, it is worth underlining that in the control group, characterised by the absence of digestive symptoms, the mean FC value was 81.5 μg/g, what is slightly elevated value in healthy infants, but compatible with other studies performed in children less than one year [10, 13, 14]. To sum up, a high calprotectin concentration in feces appears to be a normal phenomenon in infants and may be related to the immaturity of adaptive immunity in infancy and inability to regulate the microbial flora in the gut [2]. However, when we analyzed FC levels in relation to the main diagnosis, we only found significant differences between investigated and control group of children. It could be explained by the comparable degree of inflammation in the digestive tract, regardless of the cause of the inflammation.

FC concentration seems to be also age-dependent in infancy [10] and according to the different study, FC levels are higher in the first month of life because of immaturity of intestinal epithelial barier function and inability to regulate the microbiota in the gut [15, 16]. Because of this data, we excluded from the analysis children aged less than one month.

Some investigators reported higher FC levels in exclusively breast-fed infants up to 3 months of age [17]. In our investigated group of children, 75.6% of them were breast-fed during the first 3 months of life. Some researches indicate the impact of probiotcs on the FC concentration. Baldassare *et al.* showed the reduction of such concentrations after the dietary treatment with extensively hydrolyzed formula with *Lactobacillus GG* than with the formula alone [15]. So, the treatment with probiotics up to two weeks before hospitalization was one of the exclusion criteria to our study.

The gut immune system is an important regulator of immune-mediated diseases, so increased values of FC have been reported not only in children with inflammatory bowel disease, but also with food allergy, but the data respecting this relationship are limited [4, 13]. In paper published by Beser *et al.* FC levels were higher in children with non-IgE-mediated cow's milk allergy than in controls [18]. Other investigations conducted on the group of patients with atopic dermatitis suggested that elevated fecal calprotectin level as a gastrointestinal inflammatory marker might be useful for assessment of severity of childhood atopic dermatitis [19].

In our study, we presented a high prevalence of food allergy in children younger than 3 years with respect to the increased FC level, expressed in the form of gastrointestinal symptoms as bleeding from GI tract, diarrhea, feeding difficulties. The most important cause was allergy to cow's milk proteins. The diagnosis of milk allergy was established on the basis of clinical symptoms and recovering of symptoms after dairy free diet and the FC level has been assessed at the time of diagnosis. We admitt that the best way to prove the impact of allergic colitis on the level of FC concentration is oral food challenge [16]. The assesment of FC should be repeated after 4–6 weeks of the dietetary treatment and followed by oral food challenge, so we are aware that further research is nedeed. It is known that a lot of patients with milk allergy achieve the tolerance to milk proteins up to 2–3 years of age and resolve spontaneously within a short period of time [13, 20]. On the other hand, it is not easy to get the parents' consent for oral food challenge in infants, who have experienced improvement. For this reason, in most of our investigated children, the food challenge has been performed after the therapeutic diet, not to confirm diagnosis but to assess the acquisition of food tolerance.

Interesting study was conducted by Belizon *et al.* on the group of infants with symptoms of non-IgE-mediated cow's milk allergy. The FC concentration was measured after one and three months of dietary treatment. In opinion of the investigators, FC levels lower than 138 μg/g could be useful to rule out non-IgE-mediated cow's milk diagnosis. Finally the authors concluded that, although there was a statistically significant relationship between FC levels and CMA, however it was not good test to predict clinical response to milk withdrawal [13]. The same conclusions come from study performed by Ataee *et al.* in the group of breast-fed infants with milk allergy. This study showed that changes on fecal calprotectin levels are not a good indicator for assessment of clinical improvement in food allergy, because there was no statistically significant difference between the fecal calprotectin levels on admission, two weeks and six weeks after milk-free diet for mothers [21].

Cow's milk, soya beans, egg, rice and wheat proteins are the most commonly reported offending foods being the cause of increased permeability of the immature mucosa leading to clinical symptoms [7, 8]. In our study, IgE-mediated allergy was diagnosed mostly to egg white and codfish.

Some researches demonstrated the connection between gut microbiota and concentration of FC as an in-

flammatory marker [22]. In the present study the main causes of infection were *Staphylococcus aureus* and *Klebsiella oxytocyta.* From the other hand, some investigators have shown that the changes in the gut microbiota and intestinal inflammation have been associated with the development of allergic diseases as food allergy or atopic dermatitis [23, 24].

Interesting observations have been made regarding the impact of gastrointestinal bleeding on the higer concentration of FC. Because neutrophils are also present in the blood and FC is the protein released by them into the intestinal lumen, so it is possibile to find higher levels of FC in the presence of bleeding [16]. It should be remembered that GI bleeding may be the result of inflammation as well as allergy. In our study we compared the levels of FC in patients with inflammation and allergy and the frequency of bleeding was comparable between groups, so it was not probably affected the mean concentration of FC. Secondly, the cited and others study concerned preterm infants, who can not be referred to healthy and older infants [16, 25].

In our study, we expected that the concentration of FC would be higher in patients with allergy compared to those with infection and that the coexistence of allergy and infection increase the concentration of calprotectin. The obtained results showed that the differences were not statistically significant.

We are aware that this study have some limitations. First of all, it is the retrospective study and although 50 μg/g was suggested as a cut-off value of FC in healhty patients, FC levels in children up to 3 years of age were not definitely proposed. Secondly, the diagnosis of milk allergy and to other than milk foods was stated on the basis of clinical symptoms and observation. Thirdly, concomitant diseases as atopic dermatitis could be one more reason for elevated values of FC in all investigated groups. Seo *et al*. conducted the study on the group of 65 children and proved that elevated FC levels were associated with severity of atopic dermatitis [19]. In our study, more than 20% of patients in each group, besides GI manifestation, had atopic dermatitis which could probably have the impact on the FC level.

Lastly, the follow-up study should be performed in children with food allergy and infection, with simulatneously assessment of the calprotectin concentration to evaluate whether these concentration normalized over time. Moreover, some authors suggest that high FC level in infants can predict asthma and atopic dermatitis by the age of 6 years [26], so further observation of the course of allergy would be interesting.

Therefore, according to our results, we can conclude that calprotectin is not specific neither for allergic enterocolitis and for GI infection and further researches should be conducted for biomarkers of allergic enterocolitis. Promising results concern the diagnostic value of eosinophil-derived neurotoxin, beacause simple and non-invasive tests are needed in pediatric care [27].

CONCLUSIONS

Food allergy as well as infection can be a cause of increased FC concentration. FC might only be useful as a screening test of allergic enterocolitis in infants and young children.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Striz I, Trebichavsky I. Calprotectin – a pleiotropic molecule in acute and chronic inflammation. Physiol Res 2004; 53: 245-253.
2. Li F, Ma J, Geng S, et al. Fecal calprotectin concentrations in healthy children aged 1-18 months. PloS ONE 2015; 10: e0119574.
3. Carroccio A, Iacono G, Cottone M, et al. Diagnostics accuracy of fecal calprotectin assay in distinguishing organic causes of chronic diarrhea from irritable bowel syndrome: a prospective study in adults and children. Clin Chem 2003; 49: 861-867.
4. Cho J, Ran Yang H. Fecal calprotectin as a reliable marker for differentiating inflammatory bowel disease from food allergy and functional abdominal pain in children. J Pediatr Gastroenterol Nutr 2017; 65: pS30.
5. Chen CC, Huang JL, Chang CJ, et al. Fecal calprotectin as a correlative marker in clinical severity of infectious diarrhea and usefulness in evaluating bacterial or viral pathogens in children. J Pediatr Gastroenterol Nutr 2012; 55: 541-547.
6. Duman M, Gencpinar P, Bicmen M, et al. Fecal calprotectin: can be used to distinguish between bacterial and viral gastroenteritis in children. Am J Emerg Med 2015; 33: 1436-1439.
7. Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome and allergic proctocolitis. Allergy Asthma Proc 2015; 36: 172-184.
8. Feuille E, Nowak-Węgrzyn A. Definition, etiology, and diagnosis of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol 2014; 14: 222-228.
9. Skiba A. Boznański A. Food protein-induced enterocolitis syndrome – a little-known form of non-IgE-mediated food hypersensitivity. Pediatr Pol 2018; 93: 270-274.
10. Fagerberg UL, Loof L, Merzoug RD, et al. Fecal calprotectin levels in healthy children studied with an improved assay. J Pediatr Gastroenterol Nutr 2003; 37: 468-472.
11. Sykora J, Siala K, Huml M, et al. Evaluation of faecal calprotectin as a valuable non-invasive marker in distinguishing gut pathogens in young children with acute gastroenteritis. Acta Paediatr 2010; 99: 1389-1395.
12. Davidson F, Lock RJ. Paediatric reference ranges for faecal calprotectin: a UK study. Ann Clin Biochem 2017; 54: 214-218.
13. Belizon TC, Ortega Paez E, Medina Claros A, et al. Faecal calprotectin as an aid to the diagnosis of non-IgE mediated cow's milk protein allergy. An Pediatr 2016; 84: 318-323.
14. Oord T, Hornung N. Fecal calprotectin in healthy children. Scand J Clin Lab Invest 2014; 74: 542-547.
15. Baldassarre ME, Laforgia N, Fanelli M, et al. Lactobacillus GG improves recovery in infants with blood in the stools and presumptive allergic colitis compared with extensively hydrolyzed formula alone. J Pediatr 2010; 156: 397-401.
16. Campeotto F, Kalach N, Lapillonne A, et al. Time course of fecal calprotectin in preterm newborns during the first month of life. Acta Paediatr 2007; 96: 1530-1535.

17. Savino F, Castagno E, Calabrese R, et al. High fecal calprotectin levels in health exclusively breast-fed infants. Neonatol 2009; 97: 299-304.
18. Beser OF, Sancak S, Erkan T, et al. Can fecal calprotectin level be used as a marker of inflammation in the diagnosis and follow up of cow's milk protein allergy? Allergy Asthma Immunol Res 2014; 6: 33-38.
19. Seo SC, Ahn SH, Ri S, et al. Elevated fecal calprotectin levels are associated with severity of atopic dermatitis in children. Asian Pac J Allergy Immunol 2018; 36: 82-87.
20. Pohl J, Azuma L, Watts M, et al. Fecal calprotectin and cow's milk protein allergy in infants. J Pediatr Gastroenterol Nutr 2005; 41: 515.
21. Ataee P, Zoghali M, Nikkhoo B, et al. Diagnostic value of fecal calprotectin in response to mother's diet in breast-fed infants with cow's milk allergy colitis. Iran J Pediatr 2018; 28: e66172.
22. Maslowski KM, Mackkay CR. Diet, gut microbiota and immune responses. Nat Immunol 2011; 12: 5-9.
23. West CE, Rydén P, Lundin D, et al. Gut microbiome and innate immune response patterns in IgE-associated eczema. Clin Exp Allergy 2015; 45: 1419-1429.
24. Merras-Salmio I, Kolho KI, Pelkomen AD, et al. Markers of gut mucosal inflammation and cow's milk specific immunoglobulins in non-IgE cow's milk allergy. Clin Transl Allergy 2014; 4: 4-8.
25. Baldassarre ME, Fanell M, Lasorella ML, et al. Fecal calprotectin (FC) in newborns: is it a predictive marker of gastrointestinal and/or allergic disease? Immunopharmacol Immunotoxicol 2011; 33: 220-223.
26. Orivouri L, Mustonen K, de Goffau MC, et al. High level of fecal calprotectin at age 2 months as a marker of intestinal inflammation predicts atopic dermatitis and asthma by age 6. Clin Exp Allergy 2015; 45: 928-939.
27. Roca M, Rodrigez Varela A, Donat E, et al. Fecal calprotectin and eosinophil-derived neurotoxin in healthy children between 0-12 years. J Pediatr Gastroenterol Nutr 2017; 65: 394-398.