

REVIEW

Indian J Allergy Asthma Immunol 2010; 24(2) : 99-106

Non-IgE Mediated Food Allergies

Savina Aneja¹, Summit Shah²

¹University Hospitals Case Medical Center, Case Western Reserve University, School of Medicine, Cleveland, Ohio and ²Will Country Medical Associates, Joliet, Illinois

Abstract

Immunologic gastrointestinal reactions involving IgE antibodies, mast cell degranulation, and the subsequent release of histamines and cytokines are fairly well understood. By contrast, the mechanisms underlying non-IgE mediated food allergies are less clear. Non-IgE mediated food allergy was first described in 1940, but due to the delayed onset of symptoms the diagnosis remains challenging in modern clinical practice. This review discusses the epidemiology, evaluation and treatment course for food protein induced enterocolitis syndrome (FPIES), dietary protein proctocolitis, dietary protein enteropathy, and celiac disease in order to aid in the diagnosis and treatment of these non-IgE mediated pathologies. Allergic eosinophilic esophagitis, allergic eosinophilic gastritis, allergic eosinophilic gastroenterocolitis are considered to be mixed IgE and non-IgE mediated pathologies. Hence, purely non-IgE mediated disorders are included in this article.

Key words: Protein enteropathy, Celiac disease, Protein induced enterocolitis, Protein proctocolitis, Food allergies

INTRODUCTION

The non-IgE mediated food allergies comprise a group of pathologies that most commonly present in young children and infants with complaints of non-specific gastrointestinal symptoms (vomiting,

abdominal distention, diarrhea). It is thought that a defect in intestinal barrier or immunologic function coupled with the period of immunologic susceptibility experienced by growing infants give rise to these pathologies.¹ Greater intestinal permeability and a functionally immature intestinal epithelial barrier are seen in infants as compared to adults may also account for the prevalence of these pathologies in the young. Further, the induction of tolerance at a young age (2 to 3 years old) may be related to gut maturation and more strict regulation of immunologic mechanisms. Nod1 (nucleotide oligomerizing domain

Address for correspondence: Dr. Summit Shah, University Hospitals Case Medical Center, Case Western Reserve University, School of Medicine, Cleveland, Ohio, E-mail: shah.summit@scrippshealth.org, IJAAI, 2010, XXIV (2) 99-106.

receptor) polymorphism has been linked to IgE mediated food allergy, but no such genetic correlation has been implicated in non-IgE mediated allergies, with the exception of celiac disease, which is a well studied gluten sensitive enteropathy caused by T-cell activation following the deamidation of gliadin.^{2,3}

It is possible to differentiate the four types of non-IgE mediated food allergies based on the chief complaint and onset of symptoms. Each pathology is associated with unique biopsy findings, although histopathological specimens are not essential in the diagnosis of food protein induced enterocolitis syndrome (FPIES), dietary protein enteropathy, or dietary protein proctocolitis (Table 1). Generally, a

specific diagnosis can be made based on the clinical features, antibody screening, and a monitored oral challenge, also known as an oral provocation test (OPT). The diagnosis of celiac disease stands out among the non-IgE mediated food allergies as it requires an intestinal biopsy.⁴

CELIAC DISEASE

Of the non-IgE mediated food allergies celiac disease is by far the most prevalent as it may affect up to 1% of the population.⁵ Few reports suggest the prevalence to be between 1 in 300 to 1 in 3700 of people. This range maybe partly attributed to the steady occurrence of subclinical, asymptomatic

Table 1. Characteristic features of the non-IgE mediated food allergies^{1,12,16,29,32,34,36}

	Age of Onset	Causative Agents	Clinical Features	Biopsy Findings
Celiac Disease	- Any age following the introduction of gluten to diet - Mean age of onset: 8 years	Gliadin fraction of gluten (alcohol-soluble protein), commonly found in wheat, rye, barley, oats	Chronic diarrhea, failure to thrive, malabsorption, abdominal distention, anemia, pallor	- Loss of absorptive villi, crypt hyperplasia, cellular infiltrate - CD8+ T-cells in the intraepithelial space, increase in [gamma]/[delta]-T cells in the jejunal mucosa
Dietary Protein Enterocolitis (FPIES)	- Birth to 12 months - Mean age for solid proteins: 5.5 months - Mean age for milk proteins: 1 month	- Cow's milk, soy milk, rice, fish, poultry, - Breast milk proteins	- Vomiting 1-3 hour and diarrhea 5-8 hours after exposure to causative agent - Irritability, abdominal distention, diarrhea, failure to thrive	Small intestine: elevated plasma cells, eosinophils, and mast cells, edema, flattened villi
Dietary Protein Enteropathy	Birth to 2 years	Cow's milk, soy milk, cereal, egg, fish	- Steatorrhea, diarrhea, malabsorption, anemia, edema - Vomiting and diarrhea 40-72 hours after exposure to the causative agent	Patchy villous atrophy, thinning mucosa and intraepithelial lymphocytes
Dietary Protein Proctocolitis	- Birth to 6 months - Frequently seen between 2-8 weeks	Breast milk proteins, cow's milk, soy milk, egg	- Blood streak, soft stools or overt rectal bleeding - Normal appearance and growth - Infrequently: anemia, hypoalbuminemia	Eosinophilic infiltrate, focal lymphoid follicle hyperplasia, lymphoid nodular hyperplasia

presentations of celiac disease, which has been well documented.⁶ HLA-DQ2 and HLA-DQ8 are found in 98% of those with confirmed celiac disease, although most carriers of DQ2 and DQ8 will never develop clinically recognized disease.¹ Associations with Down syndrome, selective IgA deficiency, and autoimmune diseases (diabetes mellitus, thyroid disease, dermatitis herpetiformis) are frequently reported.^{1,7}

Celiac disease is more commonly seen in females and can present at any age, although it is often thought to be a diagnosis of childhood. In recent years, the mean age at diagnosis has increased best demonstrated by an epidemiological study of Telega et al. in which the mean age at diagnosis was 5.32 years prior to 1995, but as of 2008 had risen to 8.70 years.⁸ Similar results were obtained in a Turkish study by Kuloglu and colleagues, where the mean age of onset was 8.81 years $\pm$ 4.63 years.³

The classical triad of celiac disease includes failure to thrive, chronic diarrhea, and evidence of malabsorption, but patients can present with a variety of symptoms (osteoporosis, anemia). Gastrointestinal complaints are more common in younger patients, whereas children over the age of 3 and adults often present with non-gastrointestinal indications.⁸ The biopsy findings of celiac disease are well described in literature and include extensive loss of absorptive villi, crypt hyperplasia, and cellular infiltrate.^{7,9} Additional findings include CD8+ T-cells in the intraepithelial space and an increase in [gamma]/[delta]-T cells in the jejunal mucosa and the peripheral blood. Additionally, extraintestinal symptoms like low bone mineral density and oral ulcers are common.³

Perhaps one of the most appreciable findings in celiac disease is the presence of anti-gliadin, and anti-endomysium antibodies, as well as tissue transglutaminase (tTG). Investigations have shown the enzymatic modification of gliadin epitopes by tTG, important in T-cell induced inflammation in the intestine, which underscores the utility of tTG in the diagnosis of celiac disease. A positive finding of anti-tTG should be followed by a small bowel biopsy to

look for evidence of villous atrophy, when a patient remains on an unrestricted diet. Confirmation of the diagnosis is ascertained if the small bowel biopsy shows histological evidence of repair following the implementation of a gluten free diet. At least four biopsy specimens must be obtained and examined from the endoscopic procedure.^{1,9,10} Duodenal biopsies can be graded according to the Marsh criteria or morphometry.¹¹

Anti-glycan antibodies have also been found associated with untreated celiac disease, but tTG IgA remains one of the most powerful tools for diagnosing celiac disease with a high sensitivity (>90%), specificity (>95%), positive predictive value, and negative predictive value.^{12,13} It has been suggested that anti-glycan antibodies may have greater clinical value as a marker of dietary adherence in patients with well established celiac disease as they are only seen in untreated celiac disease.¹³ Recently antibodies against synthetic deamidated gliadin peptides have been introduced as tool for the diagnosis of celiac disease, but due to the novelty of these synthetically derived peptides anti-endomysial antibodies and tTG IgA measured with ELISA or multiplex immunoassay are the preferred tools for screening and diagnosis.^{12,14} Vivas et al (2009) reported that strongly positive (>30 U) anti-tTG should be sufficient in the diagnosis of celiac disease in children; however in adults a duodenal biopsy is necessary to confirm a diagnosis because adults more often have a lower tTG titer. Based on these findings, it has been proposed that in children with strongly positive anti-tTG findings biopsy should be performed only when symptoms do not respond to dietary modifications.¹⁵ It is unclear if their findings will make a significant difference in the evaluation of patients presenting to pediatric gastroenterology clinics.

Once a diagnosis has been established the treatment for non-IgE allergies involves avoidance of the causative agent. In celiac disease lifelong avoidance of gluten containing grains (barley, rye, wheat, oats) typically alleviates symptoms.¹ Despite the resolution of symptoms, celiac patients are at increased risk for the development of gastrointestinal

neoplasms like adenocarcinoma of the small bowel and enteropathy-associated T-cell lymphoma. Consequently, celiac patients should be examined vigilantly, when present with abdominal pain while adhering to a gluten restricted diet.⁹

FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME

Like celiac disease, food protein induced enterocolitis syndrome (FPIES), is a gastrointestinal food allergy, which is thought to be mediated by an inappropriate T-cell response. Common food triggers include cow's milk, soy milk, and rice, although specific proteins have not been isolated as in celiac disease. Milk protein and rice are the most frequently cited causative agents, but there are reports of FPIES following the consumption of solid foods including peanut, egg, poultry (turkey, chicken) and vegetables (peas, sweet potato, squash, string beans).^{16,17} The median age of onset varies based on the trigger or causative agent. The median age of onset for cow or soy milk induced FPIES is 1 month, whereas for solid food induced FPIES the median age is 5.5 months.^{16,18} There is slight male predominance (60% male) and 25% have concurrent atopic dermatitis. The estimates indicate that 75% have a family history of atopy and 20% have a family history of food allergy.^{19,20}

FPIES most frequently presents acutely with vomiting. Severe cases of FPIES often resemble sepsis as 20% of acute exposures are associated with hypovolemic shock.²¹ In a study by Nowak-Węgrzyn et al. 57% of infants diagnosed with FPIES underwent sepsis evaluation and 64% were hospitalized due the severity of shock or dehydration.¹⁶ Additional features of FPIES include: lethargy, hypoalbuminemia, failure to thrive, and pallor.² In a retrospective study by Mehr and colleagues decreased body temperature and thrombocytosis were seen in 24% and 63% of FPIES patients, respectively.¹⁸ Stool specimens can show the presence of occult blood, polymorphonuclear neutrophils, eosinophils, and Charcot-Leyden crystals. Small intestine biopsies reveal elevated number of plasma cells, eosinophils, and mast cells, edema, flattened villi. while colon specimens show crypt

abscesses and diffuse inflammatory cell infiltrates.^{7,17} A study has correlated the severity of inflammation present in intestinal mucosa with an increased recovery of lactulose and decreased passage of mannitol, which are indicative of impaired intestinal barrier function, although this kind of workup is not recommended for routine clinical diagnosis of FPIES.²²

A review of 14 infants with FPIES in 2003 suggested that breast-feeding had a protective effect against FPIES as it was not diagnosed until patients began consuming other products.¹⁶ However, FPIES stemming from food proteins passed in breast milk have been reported infrequently, so this should also be considered in breast fed infants.⁷

Most infants outgrow FPIES by the age of 3, which is thought to be due to the establishment of oral tolerance in the gut mucosal immune system.^{2,18} The median age of tolerance is 24 months for solid food induced FPIES and 28 months for cow's milk induced FPIES, with few exceptions. Remedy in soy induced FPIES is less readily achievable, as 70% remain intolerant after 3 years of age.^{16,18} In most infants, hydrolyzed casein formulas are tolerated as substitutes for cow's milk or soy milk when treating FPIES, dietary protein proctocolitis, and dietary protein enteropathy. Those do not respond well to hydrolyzed casein formulas can usually tolerate amino acid based formula.^{7,21,23} As many as 50% of patients determined to be sensitive to cow's milk protein will also have a reaction to soy milk protein, so it is generally not recommended as a substitution. Because of the risk of solid-food protein induced FPIES, it is suggested to delay the introduction of grains as solid foods in infancy, unless already tolerated by the patient.^{7,19}

In the treatment of acute FPIES presenting with shock, intravenous fluid resuscitation is advised. Epinephrine, used in the treatment of IgE mediated food allergy, is not recommended for the acute treatment of non-IgE mediated allergy presenting with shock. Some parents of patients appreciate obtaining a letter from their physician that explains the condition requiring emergent care in the event of accidental ingestion.^{18,19}

DIETARY PROTEIN ENTEROPATHY

Dietary protein enteropathy closely resembles FPIES clinically, but should be considered a distinct pathology. Common causative agents include cow's milk, soy milk, cereal, egg and fish. The onset of symptoms can appear as late as two years of age, although most patients present symptomatically within the first 3 months of life.^{7,24,25} The exact prevalence is not known but it is often seen in patients with IgA immunodeficiency or atopy, and has been linked to early bottle feeding.²⁶

Lyngkaran et al. proposed a diagnostic criteria for cow's milk protein sensitive enteropathy in 1978, although it had long been recognized as a cause of malabsorption and diarrhea in infants.²⁴ Now it is widely accepted that clinical diagnosis of dietary protein enteropathy can be made on the presentation of diarrhea (with or without vomiting), while consuming cow's milk protein, and the appearance of clinical or histological improvement following 6 to 8 weeks on an exclusion diet. Diarrhea, failure to thrive, and vomiting are common features, but atopic eczema and recurring respiratory infections are also reported in as many as 20% cases.²⁷ The reports suggest that symptoms of malabsorption may take up a month to develop in infants given that the onset of symptoms correlate with the severity and extent of mucosal damage in the intestine.^{24,27} In cases where the causative agent was cow's milk, serum IgA and IgG antibodies to cow's milk proteins were elevated. The proximal bowel biopsy specimens reveal patchy villous atrophy, thinning mucosa, increased crypt length and intraepithelial lymphocytes.²⁶ An oral food challenge can be used to distinguish between dietary protein enteropathy and FPIES based on the onset of symptoms. In FPIES vomiting is observed within 1 to 3 hours and diarrhea within 5 to 8 hours from the time of exposure. Conversely, in dietary protein enteropathy vomiting and diarrhea are not present until 40 to 72 hours after exposure to the causative agent.⁷

Clinical symptoms usually resolve within 3 to 21 days following the elimination of the antigen from the diet. Tolerance usually develops within one to two years of life, although biopsies at this time may still

show abnormalities. It has been demonstrated that only 29% of infants present with normal mucosa despite the resolution of symptoms around the age of one in cases of cow's milk intolerance.^{26,27}

DIETARY PROTEIN PROCTOCOLITIS

Dietary protein proctocolitis, referred to as allergic proctocolitis, is also one of the non-IgE mediated food allergies, and is symptomatically distinct from the other pathologies in this group, as it presents primarily with blood streaked stools in otherwise well appearing patients. Dietary protein-induced proctocolitis is considered a common cause of proctocolitis in infancy, but can be seen in older children as well. The exact prevalence is unknown but in one series of 22 infants with rectal bleeding protein-induced proctocolitis, it was determined to be the cause in 64% of patients, whereas in other series of 40 infants, a diagnosis of protein-induced proctocolitis was made in only 18% of cases.^{23, 28} Nearly 60% of infants who present with proctocolitis are breast fed at the initial phase, and much of the remaining appear to be affected by cow's milk or soy milk based formulas.²¹ Ravelli et al. determined dietary protein proctocolitis to be the second most common cause of overt rectal bleeding, with a mean age of onset at 7.5 years in pediatric population.²⁹ Family history of atopy was variable in both infant and pediatric populations.^{29,30}

Dietary protein proctocolitis patients are usually well-appearing, normal growing infants. Blood loss in stool can sometimes impart a mild anemia that is usually an incidental finding.^{7,21} In children proctocolitis can sometimes present with reportedly mild and occasional gastrointestinal symptoms like diarrhea, vomiting, constipation and abdominal pain.²⁹ The left colonic mucosa is most frequently implicated in proctocolitis. Findings of eosinophilic infiltrate and focal lymphoid follicle hyperplasia are typical, and in 20% of patients there is evidence of lymphoid nodular hyperplasia.^{7,29}

Removing cow's milk protein from the lactating mother's diet or replacing the infants formula results in improvement of symptoms within 48 to 72 hours. When exclusion of cow and soy milk protein from the

lactating mother's diet fails, the symptoms will usually respond to use of a casein hydrolysate or amino acid based formula. Often a failure to respond to maternal exclusion diet is due to the inability to remove all sources of cow's milk and soy milk from the maternal diet. In infant onset protein-induced proctocolitis, tolerance to cow's milk protein developed within a year. In older children an exclusion diet relieves symptoms within 1 to 7 days.^{21,23} In childhood onset disease, tolerance within a year was less appreciable (<50%) as 6 of 16 patients remained on a cow's milk free diet for many years since attempts to reintroduce cow's milk protein resulted in overt rectal bleeding.²⁹

Patient education is a vital component in recovery as complete avoidance of the offending food allergen is the most effective therapy until tolerance is established. In addition to follow up with an allergist, the patient should be encouraged to consult a nutritionist to ensure the age appropriate nutritional requirements and preventable dietary deficiencies.⁴

CHALLENGES IN PATIENT EVALUATION

Evaluating a patient for non-IgE mediated food allergy has proven to be quite cumbersome, partly due to the delayed onset of symptoms, which can occur hours to days after exposure to the antigen.² Nevertheless, non-IgE mediated allergy should be included in any differential diagnosis of an infant or young child presenting with gastrointestinal symptoms. Mehr et al. in a retrospective study demonstrated that, of 19 episodes of FPIES, presenting to the Emergency Department, only 2 were correctly diagnosed at the initial presentation. Delayed diagnoses were made following unnecessary investigational testing that ranged from abdominal imaging to laparotomy.¹⁸

The vomiting and diarrhea experienced as a result of a non-IgE mediated food allergy can manifest in severe complications of hypotension like shock, acidemia and methemoglobinemia which often point toward a diagnosis of sepsis. In addition to sepsis, the differential diagnosis includes: IgE mediated food allergy, bacterial gastroenteritis, lactose deficiency, gastritis, inflammatory bowel

disease, parasitic infections, anal fissure, incomplete duodenal atresia, and intussusception. Infectious and obstructive pathologies can most often be ruled out with blood tests, stool culture or smear, and abdominal imaging. The absence of food allergen specific IgE, negative skin prick test, and a lack of respiratory or dermatological involvement support the diagnosis of a non-IgE mediated food allergy.^{2,16}

A patient's past medical history can be useful in the diagnoses of food allergies, but is often less fruitful in establishing a diagnosis of non-IgE mediated food allergy as the reactions are often delayed or subacute. Food diaries can be helpful, although they are often unreliable and cumbersome to the patient. Diagnostic elimination diet, whereby the patient removes a selected item from their diet and waits for the appearance of symptoms can be unreliable as patients may not be aware of all the ingredients in their meals. Oral challenges are reliable, but risky unless they are conducted under observation with an intravenous line in place. In the absence of sensitive and specific serological markers, a trial of avoidance and a challenge test under the supervision of a clinician is thought to be the gold standard for diagnosing many of the non-IgE mediated allergies.²

Well supervised oral challenges can be used to determine, when causative agents can be reintroduced into the diet in patients with FPIES, dietary protein enteropathy, or dietary protein proctocolitis. However, challenges should only be carried out when the patient is stable, asymptomatic, and normal gaining weight.²⁶ It is recommended to wait 18 months post reaction to perform challenges in infants. During an oral protein challenge a recommended dose of 0.15-0.3 grams of protein per kilogram of body weight is administered gradually over a period of 45 minutes. In the absence of symptoms an additional dose can be administered in 4 hours, followed by additional observation.¹⁹ Prompt administration of intravenous fluids and steroids is recommended to control the symptoms developed during the challenge. Based on the Powell's criteria, a challenge is considered positive if 3 or more of these are observed: rise in PMN count, fecal blood,

fecal leukocytes, fecal eosinophils, vomiting or diarrhea.³¹

It was thought that increases in IgG4 measured by enzyme-linked immunosorbent assay (ELISA) or radioallergosorbent test (RAST) could be used to determine delayed responses to food allergens and may be of value in the diagnosis of non-IgE mediated food allergies.³⁰ However, in studies by Jenkin and Vickers and Roger et al, no evidence was found to strongly support the use of IgG4 antibody as a diagnostic tool.^{32,33} Additionally, there are multiple reports of positive IgG4 that do not correlate appreciably with clinical symptoms, and positive IgG4 results for foods never consumed by the patient under study.^{32,34} While some of these results can be attributed to cross reactivity and de-sensitization, in general IgG4 assays are of no diagnostic value in clinical practice.

CONCLUSION

The non-IgE mediated food allergies represent a group of well documented pathologies that should be included in the differential diagnosis of any patients presenting with non-specific gastrointestinal complaints. Despite estimates that up to 50% of pediatric cow's milk allergy is non-IgE mediated these pathologies may be overlooked in clinical practice. Erroneous and delayed diagnosis can result in unnecessary medical testing and leave patients vulnerable to serious complications including hypotension and shock. The available diagnostic criteria have made diagnoses straightforward; however we still lack a single effective laboratory test to streamline assessment, so clinical suspicion remains paramount. Because the Pathophysiology of non-IgE mediated food allergy is poorly understood, more has to be learned about the chemical mediators, host immune response and multidirectional pathways. The development of innovative and effective testing methods will unequivocally extend the frequency of diagnosis and expand the scope of the clinical management of these pathologies.

REFERENCES

1. Faulkner-Hogg K, Hodge L, Swain A. Coeliac disease. *Australian Family Physician*. 2009; **38**: 785-86.
2. Jyonouchi H. Non-IgE mediated food allergy. *Inflammation Allergy-Drug Targets*. 2008; **7**: 173-180.
3. Kuloglu Z, Kirsaciloglu CT, Kansu A, Ensari A, Girgin N. Celiac disease: presentation of 109 Children. *Yonsei Med J*. 2009; **50**: 617-23.
4. Malterre T. Digestive and nutritional considerations in celiac disease: could supplementation help? *Altern Med Rev* 2009; **14**: 247-57.
5. Murray JA, Rashtak S, Rubio-Tapia A. Diagnosis of celiac disease in pediatric patients. *Nat Rev Gastroenterol Hepatol* 2009; **14**: 247-57.
6. Cavell B, Stenhammar L, Ascher H, et al. Increasing incidence of childhood celiac disease in Sweden. Results of a national study. *Acta Paediatr*. 1992; **81**: 589-92.
7. Sampson HA, Anderson JA. Summary and recommendations: Classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. *J Pediatr Gastro Nutr*. 2000; **30 Suppl**: S87-94.
8. Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in the presentation of celiac disease. *Arch Pediatr Adolesc Med*. 2008; **162**(2): 164-68.
9. Soyer P, Boudiaf M, Fargeaudou Y, et al. Celiac Disease in Adults: Evaluation with MDCT Enteroclysis. *AJR*. 2008; **191**: 1483-92.
10. Rondonotti E, Spada C, Cave D, et al. Video Capsule Enteroscopy in the Diagnosis of Celiac Disease: A multicenter study. *Am J Gastroenterol*. 2007; **102**: 1624-163.
11. Ensari A, Marsh MN, Loft DE, Morgan S, Moriarty K. Morphometric analysis of intestinal mucosa. V. Quantitative histological and immunocytochemical studies of rectal mucosae in gluten sensitivity. *Gut* 1993; **34**(9): 1225-29.
12. Basso D, Guariso G, Fogar P, et al. Antibodies against synthetic deamidated gliadin peptides for celiac disease diagnosis and follow-up in children. *Clin Chem*. 2009; **55**: 150-57.
13. Papp M, Foldi I, Altortjay I, et al. Anti-microbial antibodies in celiac disease: trick or treat. *World J Gastroenterol*. 2009; **15**(31): 3891-3900.
14. Rashtak S, Ettore MW, Homburger HA, Murray JA. Combination testing for antibodies in the diagnosis of celiac disease: comparison of multiplex

1. Faulkner-Hogg K, Hodge L, Swain A. Coeliac disease.

- immunoassay and ELISA methods. *Alimentary Pharmacol Therapeutics* 2008; **28**: 805-13.
15. Vivas S, Ruiz de Morales J, Riestra S, et al. Doudenal biopsy may be avoided when high transglutaminase antibody titers are present. *World J Gastroenterol* 2009; **15**(38): 4775-80.
 16. Nowak-Węrzyn A, Sampson H, Wood R, Sicherer SH. Food Protein-Induced Enterocolitis Syndrome Caused by Solid Food Proteins. *Pediatrics* 2003; **111**: 829-35.
 17. Nowak-Węrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol*. 2009; **9**(4): 371-77.
 18. Mehr S, Kakakios A, Frith K, Kemp AS. Food Protein-Induced Enterocolitis Syndrome: 16-Year Experience. *Pediatrics* 2009; **123**: e459-64.
 19. Sicherer SH. Food Protein-Induced Enterocolitis Syndrome: Case Presentations and Management Lessons. *J Allergy Clin Immunol*. 2005; **115**: 149-56.
 20. Sicherer SH. Food Protein-Induced Enterocolitis Syndrome: Clinical Perspectives. *J. Pediatric Gastroenterol*. 2000; **30**(1): S45-49.
 21. Maloney J, Nowak-Węrzyn A. Educational clinical cases series for pediatric allergy and immunology: Allergic proctocolitis, food-protein induced enterocolitis syndrome and allergic eosinophilic gastroenteritis with protein-losing gastroenteropathy as manifestations of non-IgE mediated cow's milk allergy. *Pediatr Allergy Immunol*. 2007; **18**: 360-67.
 22. Dupont C, Heyman MJ. Food Protein-Induced Enterocolitis Syndrome: Laboratory Perspectives. *Pediatr Gastroenterol. Nutr*. 2000; **30**: S50-57.
 23. Xanthakos SA, Schwimmer JB, Melin-Aldana h, Rothenberg ME, Witte DP, Cohen MB. Prevalence and outcome of allergic colitis in healthy infants ith rectal bleeding: a prospective cohort study. *J pediatr Gastroenterol Nutr* 2000; **30 Suppl**: S50-57.
 24. Lyngkaran N, Robinson MJ, Prathap K, Sumithran E, Yadav M. Cows' milk protein-sensitive enteropathy. Combined clinical and histological criteria for diagnosis. *Arch Dis Child*. 1978; **53**: 20-26.
 25. Lyngkaran N, Robinson MJ, Davis KA, et al. Cows' milk protein-sensitive enteropathy (CMPSE): an important cause of protracted diarrhoea in infancy. *Aust paediatr J* 1979; **15**: 266-70.
 26. Walker-Smith JA. Cow milk-sensitive enteropathy: predisposing factors and treatment. *J Pediatr*. 1992; **121**: S111-15.
 27. Kuitunen P, Visakorpi JK, Savilahti E, Pelkonen P. Malabsorption syndrome with cow's milk intolerance. Clinical findings and course in 54 cases. *Arch Dis Child*. 1975; **50**(5): 351-56.
 28. Arvola T, Ruuska T, Keranen J, Hyoty H, Salminen S, Isolauri E. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. *Pediatrics*. 2006; **117**: e760-68.
 29. Ravelli A, Villanacci V, Chiappa S, Bolognini S, Manenti S, Fuoti M. Dietary Protein-Induced Proctocolitis in Childhood. *American J Gastroenterol*. 2008; **103**: 2605-12.
 30. El Rafei A, Peters SM, Harris N, Bellanti JA. Diagnostic value of IgG4 measurements in patients with food allergy. *Ann Allergy* 1989; **62**: 94-99.
 31. Powell GK. Food protein-induced enterocolitis of infancy: differential diagnosis and management. *Compr Ther*. 1986; **12**: 28-37.
 32. Jenkins M, Vickers A. Unreliability of IgE/IgG4 antibody testing as a diagnostic tool in food intolerance. *Clin Exp Allergy* 1998; **28**: 1526-1529.
 33. Roger A, Pena M, Botey J, Esevenri JL, Martin A. The value of IgG4 determination in childhood allergy to egg in relation to specific IgE and the provocation test. *J Invest Allergol Clin Immunol* 1994; **4**: 87-90.
 34. Stapel SO, Asero R, Ballmer-Weber BK, et al. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. *Allergy* 2008; **63**: 793-796.
 35. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food-protein-induced enterocolitis syndrome. *J Pediatrics* 1998; **133**: 214-19.
 36. Heine RG. Pathophysiology, diagnosis and treatment of food protein-induced gastrointestinal diseases. *Curr Opin Allergy Clin Immunol* 2004; **4**(3): 221-29.