Review Article

Non-IgE mediated food allergy: food protein-induced allergic proctocolitis – An update

Alergia alimentar não IgE mediada: proctocolite induzida por proteínas alimentares – Atualização

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ABSTRACT

An increase in the worldwide prevalence of food allergies has been observed in the past decades, currently affecting 6% of children. This increase has been associated with the interaction between genetic, environmental, and immune response factors and can be observed in IgE, non-IgE, and mixed mediated reactions. Non-IgE mediated food allergies result from delayed-type hypersensitivity and mostly affect the gastrointestinal tract, such as food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPE), and celiac disease. These reactions can be differentiated by their clinical presentation, severity, age at onset, and natural history. Among non-IgE-mediated allergic reactions to food, allergic proctocolitis is the most frequent. It usually develops in the first year of life and has excellent prognosis. Although it has a benign course, allergic proctocolitis is challenging for health care professionals because it often presents with hematochezia, requiring an accurate differential diagnosis. Knowledge and management of allergic proctocolitis is of paramount importance for medical practice in allergy and immunology. Its diagnosis is based on clinical history followed by elimination diet, especially cow's milk, with subsequent oral food challenge, which may usually be performed at home. Accurate diagnosis is important to avoid unnecessary elimination diets. For this review, PubMed database was searched for recently published literature reviews and studies on the diagnosis and treatment of non-IgE mediated allergies, with a focus on allergic proctocolitis.

Keywords: Food hypersensitivity, infantile diarrhea, gastrointestinal hemorrhage, milk hypersensitivity, breastfeeding.

RESUMO

Nas últimas décadas observa-se aumento na prevalência mundial de alergia alimentar, que já acomete aproximadamente 6% das crianças, atribuído à interação entre fatores genéticos, ambientais e alterações na resposta imunológica e pode envolver reações mediadas por IgE, não mediadas e mistas. As formas não IgE mediadas decorrem de reação de hipersensibilidade tardia, mediada por linfócitos T e afetam prioritariamente o trato gastrointestinal, como a Síndrome da entero-colite induzida por proteína alimentar (FPIES), Síndrome da procto-colite alérgica induzida por proteína alimentar (FPIAP), Síndrome da enteropatia induzida por proteína alimentar (FPE) e doença celíaca. As características destas reações podem ser diferenciadas por sua apresentação clínica, gravidade, idade de início e história natural. Entre as reações alérgicas aos alimentos não IgE mediadas, a proctocolite alérgica é a mais frequente. Geralmente ocorre no primeiro ano de vida e apresenta excelente prognóstico. Embora costume ter um curso benigno, traz grande preocupação aos cuidadores por frequentemente cursar com quadro de hematoquezia exigindo diagnóstico diferencial adequado. O conhecimento e manejo da proctocolite alérgica é de suma importância para a prática médica em Alergia e Imunologia. Seu diagnóstico é baseado na história clínica seguindo-se dieta de exclu-são, especialmente do leite de vaca, com subsequente provocação oral, que geralmente pode ser realizada no domicílio. O diagnóstico preciso é importante, para se evitar dietas de exclusão desnecessárias. Nesta revisão foram utilizados artigos publicados nos últimos anos, com busca realizada através da base PubMed envolvendo revisões, diagnóstico e tratamento de alergias não IgE mediadas, com foco em proctocolite alérgica.

Descritores: Hipersensibilidade alimentar, diarreia infantil, hemorragia gastrointestinal, hipersensibilidade ao leite, aleitamento materno.

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Introduction

Allergic reactions to foods have been the subject of intense discussion and research among experts. In the last two decades, an increase in prevalence has been observed, with data varying between different studies, probably due to differences in their methodology, including different definitions of food allergy (AA) and eating habits in the geographical areas studied.[1] Its occurrence and clinical expression depend on the interaction between genetic and environmental factors and changes in the immune response. It affects approximately 6% of children, being more common in children under 3 years of age. In adults, a prevalence of 3.5% is estimated.[1,2] The associated family history of atopy is still the greatest risk indicator for its onset. A recent study in Brazil found that among the 604 patients with a report of AA, 4% had a confirmed diagnosis of food allergy.[3] Another study in Brazil showed an incidence of cow's milk protein allergy (CMPA) of 2.2% and a prevalence of 5.4% in children aged ≤ 24 months.[4] The knowledge and management of this condition becomes, therefore, of paramount importance for clinical practice in Allergy and Immunology.

Food allergy with gastrointestinal manifestations results from continuous exposure to food protein, which promotes inflammation by different immunological mechanisms. It can have different forms of presentation, depending on the mechanism and the location predominantly involved.

Classification

Allergic reactions to food are exacerbated immune responses to food ingestion that occur in a susceptible host.[5] These reactions can be classified, according to the type of immune response to the ingested antigens, into immunoglobulin E (IgE)-mediated, non-IgE-mediated, and mixed reactions[6] (Figure 1).

IgE-mediated reactions are usually manifested by symptoms that occur shortly after ingestion of food, usually involving the skin (urticaria, angioedema), respiratory tract (cough, wheezing, nasal congestion), cardiovascular system (hypotension), and may also present like anaphylaxis.[1]

Mixed reactions involve IgE antibodies, T lymphocytes and cytokines. They manifest as eosinophilic gastropathies (eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis), atopic dermatitis, and asthma.[7]

Non-IgE-mediated allergic reactions to foods occur without the participation of specific IgE and are due to a delayed-type hypersensitivity reaction mediated by T lymphocytes.[5,8] They are expressed by pathologies that affect various organs, such as the gastrointestinal tract, like Food Protein Induced Enterocolitis Syndrome (FPIES), Food Protein Induced Allergic Proctocolitis Syndrome (FPIAP), Food Protein Induced Enteropathy Syndrome (FPE), and celiac disease. The skin can be affected in cases of food contact dermatitis and dermatitis herpetiformis, in addition to the lungs in Heiner syndrome or pulmonary hemosiderosis (Figure 2). The expression of symptoms and severity depends on the segment of the gastrointestinal tract affected.[9] Celiac disease and iron deficiency anemia induced by cow's milk allergy are also classified as non-IgE-mediated reactions, but will not be discussed in this review.[6]

Presentation of non-IgE-mediated allergies

The main gastrointestinal manifestations of non-IgE-mediated food allergy have similar and overlapping clinical expressions, but which can be differentiated based on their typical clinical features, severity, age of onset, and natural history.[10]

Table 1 shows a comparative chart between the three main forms of non-IgE mediated food allergy: FPIES, FPIAP and FPE.

Food protein-induced proctocolitis syndrome - FPIAP

FPIAP, also called allergic proctocolitis, is a form of food allergy not mediated by IgE, which appears in the first six months of life, being more frequent between the first and fourth weeks after birth.[13] It often manifests as blood and mucus in the stool in healthy infants. More rarely, vomiting and diarrhea may occur. Onset is usually insidious, with a prolonged latent period after introduction of food, although onset may rarely be acute, within 12 hours of first contact.[14]

It is a benign and transient condition, which does not interfere with the child's growth even when the causal food remains in the diet and bleeding continues, although it can progress to anemia.[14]

In 60% of cases of hematochezia in infants, the cause is allergic proctocolitis.[15] It can affect breastfeeding children. In fact, approximately 60% of cases of proctocolitis occur in breastfeeding infants.[16] Cow's milk (VL) is the main causal food, although several foods, such as soy, egg, wheat and others,
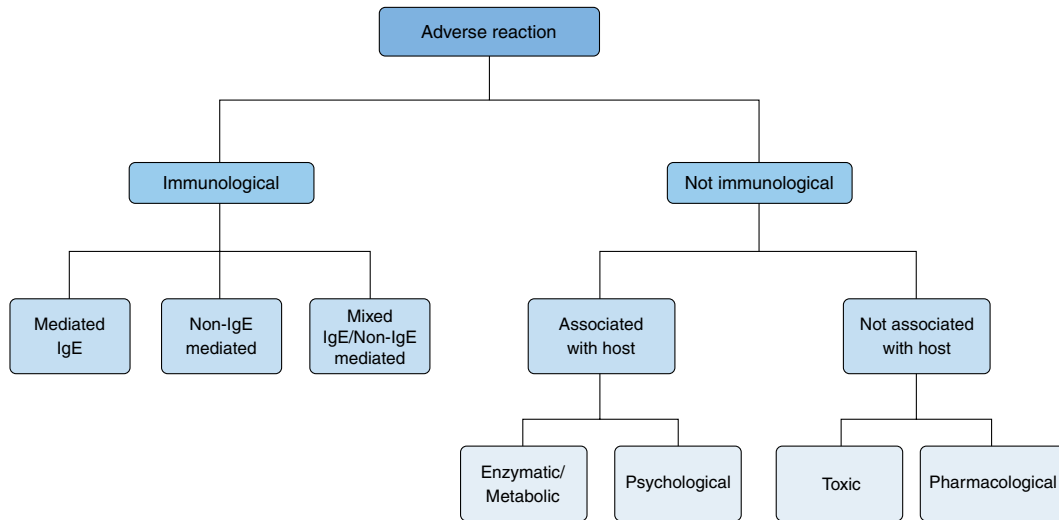
Figure 1

Classification of adverse food reactions

can be excreted in breast milk after ingestion by the mother and consequently can be considered as possible agents. Infants fed formulas containing LV or soy may also have allergic proctocolitis; including extensively hydrolyzed VL formulas, which can lead to symptoms in up to 10% of cases.[16]
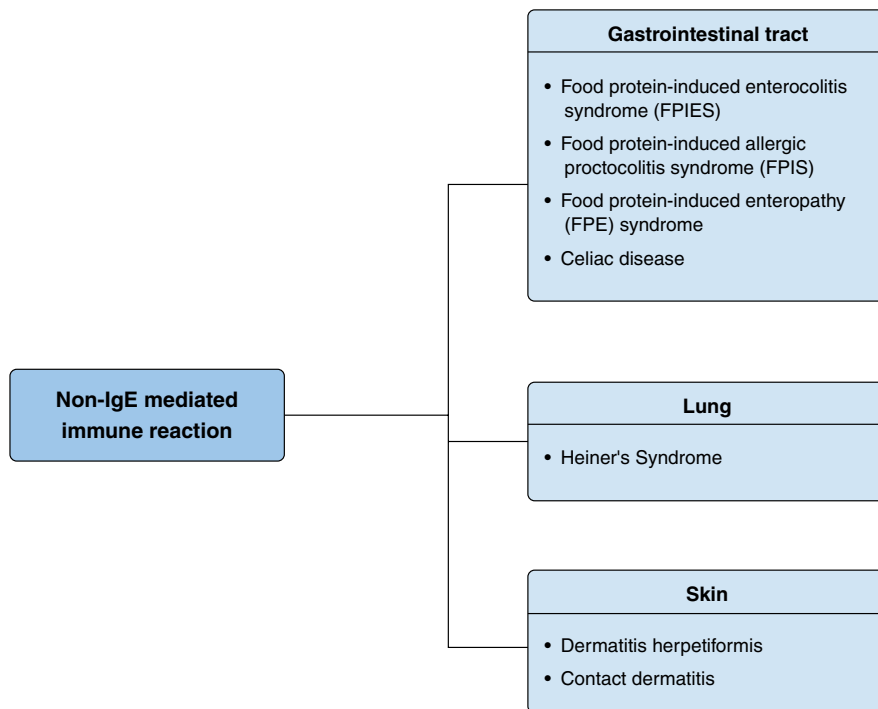
Figure 2

Non-IgE-mediated immune-mediated adverse food reactions

Adapted from: Sampson HA.[8]

Table 1

Comparison of major non-IgE-mediated gastrointestinal allergic syndromes

Features	FPIES	FPIAP	FPE
Typical age of onset	Days to 12 months	Days to 6 months	2 to 24 months
Symptoms			
Vomit	Prominent	No	Intermittent
Diarrhea	Severe	No	Moderate
Blood in the stool	Severe	Moderate	Rare
Edema	Acute, serious	No	Moderate
Shock	15-20%	No	No
Deficit weight-stature	Moderate	No	Moderate
Most typical presentation	Late and repetitive vomiting	Blood in the stool	Chronic diarrhea
Main foods involved	Milk, soy, rice	Milk, soy	Milk, soy, wheat, egg
Multiple awareness	> 50% milk/soy in some populations	40% milk/soy	Rare
Feeding at onset of symptoms	Formula	> 50% exclusive breastfeeding in some studies	Formula
Resolution age	> 3 years	1-2 years	1-3 years
Prick test with food	Negative*	Negative	Negative
Food specific IgE	Negative*	Negative	Negative
Total IgE	Normal	Normal	Normal
Peripheral blood eosinophilia	No	Occasional	No
Biopsy			
Villous lesion	Not uniform	No	Crypts of varying size
Colitis	Prominent	Focal	No
Mucosal erosion	Occasional	Occasional, linear	No
Lymph node hyperplasia	No	Common	No
Eosinophils	Prominent	Prominent	Few
Food challenge test	Vomiting in 4 to 6 hours, diarrhea in 5-8 hours	Rectal bleeding in 6-72h	Vomiting, diarrhea or both in 40-72h

FPIES = Food Protein Induced Enterocolitis Syndrome, FPIAP = Food Protein Induced Allergic Proctocolitis Syndrome, FPE = Food Protein Induced Enteropathy Syndrome.

* Positive prick test and/or specific IgE may be present at initial diagnosis or at follow-up (atypical FPIES).

Adapted from Caubet et al.[11] and Leonard AS[12].

Food protein-induced enterocolitis syndrome - FPIES

FPIES occurs predominantly in infants between 2 and 7 months of age, associated with the introduction of milk formulas and solid foods.[11] Rarely occurs in exclusively breastfed children, older children and adults.[17] In 65 to 80% of cases, FPIES is caused by a single food, mainly VL or soy. Other agents involved include egg and cereals, particularly rice and oats.[18]

The clinical expression of FPIES is influenced by the protocol of introduction of solid foods in the infant, frequency and type offood allergen introduced in the diet, in different geographic regions.[18]

FPIES is divided into two phenotypes: acute and chronic. The acute form is the most common and usually occurs by accidental ingestion, or re-exposure to the causal food after a period of restriction diet. It is manifested by uncontrollable vomiting, lethargy and pallor, which begin 1 to 4 hours after ingestion of the food involved.[19] In 15% of cases, it can progress to severe systemic symptoms that include hypothermia, hypotension, and may progress to hypovolemic shock.[20] Diarrhea can occur within 5 to 10 hours and often represents a more severe form of FPIES. The acute form is also seen in older children or adults when the causal food is not a staple food and is consumed only occasionally. In adults, it is usually associated with the ingestion of crustaceans.[12] Children with FPIES triggered by LV and soy proteins usually become tolerant around 2 to 3 years of age, whereas forms triggered by solid foods tend to have a longer evolution.[11,18]

Chronic FPIES is infrequent and is characterized by the persistence of symptoms, which, despite being less intense than those of the acute form, can be severe. The most reported symptoms are vomiting, diarrhea (with or without blood), lethargy, dehydration, abdominal distension and failure to thrive. In these situations, a differential diagnosis with inflammatory bowel diseases should be sought.[12,19]

Food protein-induced enteropathy syndrome - FPE

PEF is characterized by chronic diarrhea and recurrent abdominal pain, which can progress to weight loss and growth retardation in up to 20% of cases. Bloody stools are usually absent, but occult blood may be present in 5% of patients.[21] It starts between 2 and 9 months of age, associated with the introduction of VL formula, and less frequently of soy, egg and wheat. PEF is a transient disorder with resolution around 1 to 3 years of age. Exclusion of the causal food, followed by reintroduction after 4-8 weeks, aids in diagnosis.[22]

Colic

Infantile colic can be considered a functional disease in babies aged 1 to 4 months, which manifests with colicky abdominal pain between 4 and 6 weeks of life and regresses around 12 weeks.[23] It is a self-limiting condition characterized by recurrent and prolonged periods of incessant crying.[24] Crying paroxysms occur especially in the late afternoon and early evening, with no apparent cause. A recent systematic review showed a prevalence rate ranging from 2 to 73%, with a median of 17.7%.[25] Less than 5% of infants with colic and excessive crying have an underlying cause.[26]

The pathophysiology of infantile colic is not completely understood, although many hypotheses have been proposed, such as intestinal immaturity, hypermotility, unstable autonomic control, alterations in the intestinal microbiota, central nervous system, sleep cycle and psychosocial factors (e.g., anxiety in children). parents, which can be exacerbated by inexperience and lack of support).[27]

The presence of infantile colic, in combination with atopic dermatitis, altered stools, colitis with rectal bleeding, or gastroesophageal reflux disease (GERD), may be related to CMPA in exclusively breastfed infants.[28] The association between food allergy and childhood colic is still controversial. However, there is evidence to demonstrate that mucosal allergic responses can alter intestinal motility and nociceptive pathways to cause visceral hyperalgesia.[28,29] The gut microbiota stimulates immune system maturation, tolerance acquisition, and enteric nervous system [RHEE] development and function. Studies suggest that an aberrant intestinal microbiota can affect intestinal motor function, gas production and, thus, generate abdominal pain.[30,31]

In CMPA, the increase in the production of pro-inflammatory cytokines and neurotoxic compounds affects the enteric nervous system and causes peristaltic dysfunction and changes in the perception of physiological stimuli, such as intestinal distention and peristalsis, which are perceived as painful events.[32]

There are no robust clinical trials demonstrating the effectiveness of a food antigen restriction

diet in colicky infants.[33] In the presence of more severe colic, associated with the presence of other gastrointestinal symptoms and a personal history of atopic dermatitis, the therapeutic exclusion diet can be started, according to the type of supply.[11,28] In infants fed formulas based on cow's milk, these can be replaced by Formulas with extensively hydrolyzed cow's milk proteins for two weeks. In case of clinical improvement, the restriction diet should be continued. However, in the absence of benefit after two weeks, dietary restrictions must be lifted.[28] In nursing infants, elimination of LV for two to four weeks from the maternal diet is recommended.[22] In the presence of an evident clinical response, the restriction diet should be continued.[10]

Gastroesophageal reflux

Gastroesophageal reflux (GER) is defined as the retrograde and involuntary passage of gastric contents into the esophagus.[23] In term and preterm newborns, reflux is usually a benign process, self-limiting and without complications. It is considered as part of the physiology and gastrointestinal maturation at this stage of life and, therefore, called physiological reflux. The peak incidence of physiological GER occurs at four months of age, and 95% of infants no longer regurgitate at 12 to 14 months of age.[34] When GER is associated with other clinical symptoms or complications, such as feeding and swallowing difficulties, difficulty in gaining weight or weight loss, growth deficiency, anemia, digestive hemorrhage, respiratory and otorhinolaryngological manifestations, among others, it is called a disease of gastroesophageal reflux (GERD).[34]

The prevalence of GER and GERD varies according to the population, study design (cross-sectional or longitudinal) and diagnostic criteria (signs/symptoms or validated questionnaire). It is estimated that at the peak age of GER, around 2-4 months, prevalence rates vary between 67% and 87%[35-37] and that are 21% between 6 and 7 months of age.[36] A recent systematic review showed that in children up to 18 months, GERD symptoms are present daily in 25% of babies, with a gradual reduction and almost complete disappearance of symptoms at 12 months of age.[38] In Brazil, Costa AJF et al.observed that the prevalence of GERD in 2004 was 11.15% (89/798; 95% CI: 9.10-13.48), being higher in the first two trimesters of life: 14.62% in the first and 13.76% in the second.[39]

Several structures contribute to the antireflux barrier: the lower esophageal sphincter (LES), the angle of His, the phrenoesophageal ligament, the crural diaphragm, and the gastric rosette. The immaturity of the anti-reflux barrier mechanisms typical of the neonatal period contributes to a higher incidence of GER.[40] It is usually associated with transient lower esophageal sphincter (LES) relaxation, being influenced by genetic, environmental, anatomical, hormonal and neurogenic factors.[41] The main mechanism responsible for preventing the development of GERD is the maintenance of adequate function of the anti-reflux barrier located at the esophagogastric junction.[41] Among the mechanisms responsible for esophagogastric junction dysfunction are transient LES relaxations, reduced LES tone and anatomical distortion at the esophagogastric junction.[40]

Symptoms of GER and GERD occur due to both the volume and acid content of the refluxed material, and sometimes it is difficult to distinguish between them.[40,42] In GERD, prolonged contact of gastric acid with the esophageal mucosa intensifies local blood flow and promotes the release of prostaglandin E2, which increases the permeability of the mucosa to acid, perpetuating the inflammatory process and the presence of symptoms and complications, such as apnea, worsening of the pulmonary condition, irritability, sleep disturbance, intolerance/bad acceptance of diet, stridor, inadequate weight gain/development, abnormal posture with posterior arching, nausea, hematemesis, aspiration of gastric contents into the airways.[40]

GERD may be associated with CMPA, however, this association has not yet been established. However, a recent narrative review found an association of CMPA with GERD in 16-56% of suspected GERD cases, with persistence of gastrointestinal symptoms until VL was excluded, regardless of breastfeeding or formula.[43] Infants with CMPA present with regurgitation and vomiting indistinguishable from those associated with physiological GER or GERD, and regurgitation may be the only manifestation.This similarity of symptoms between CMPA and GER/GERD makes it difficult to distinguish the etiology of the condition, especially in the absence of other signs of allergy, such as atopic dermatitis or unexplained rectal bleeding in the first months of life.[40]

The absence of a specific symptom and/or a test considered the gold standard for the diagnosis of GERD and non-IgE-mediated CMPA, in addition to the

overlap with other functional and organic conditions and the spontaneous resolution of symptoms in the first year of life, make the diagnosis and the discrimination between APLV, GER and GERD a challenge.[44] In healthy infants with regurgitation or in those who do not respond to thickened diets and postural therapy, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) suggest that infants using LV protein formula, replacement is made with extensively hydrolyzed formula for 2 to 4 weeks; and for those who are breast-feeding, mothers should be instructed to discontinue LV protein intake for the same period. If symptom improvement occurs after the VL has been eliminated, reintroduction of the allergen is necessary to confirm the allergy.[40]

Constipation

Constipation is often associated with hardened stool consistency, an increase in the interval between bowel movements, and the occurrence of pain during bowel movements.[45] It is classified as functional in the vast majority of cases and only a small proportion of pediatric patients is associated with food allergy.[22]

Children who have a decrease in the frequency of bowel movements in the first weeks of life or after the introduction of VL-based products in the diet should be investigated for this condition.[46] In these cases, constipation is usually associated with the presence of hard stools, in addition to excessive and prolonged straining in the evacuation.[47]

The pathophysiology of the association between food allergy and constipation has not yet been fully clarified.[11] Although the results of the studies are conflicting, food allergy should be considered in the differential diagnosis of children who have persistent constipation and are resistant to conventional treatment.[46]

Diagnosis of food protein-induced constipation in breastfed infants is based on clinical improvement during the maternal elimination diet, followed by recurrence of symptoms after reintroduction of the suspected food.[22]

Food protein-induced proctocolitis - FPIAP

Epidemiology

Among allergic reactions to non-IgE food mediated, to Food protein-induced proctocolitis, better known as allergic proctocolitis, is the most frequent, although its exact prevalence is not well established.[1,6] Usually occurs in the first year of life and resolves in the first few years.[48]

Although it tends to have a benign course, it is usually of great concern to parents and guardians, and therefore deserves special attention.[49] In a prospective study, Martin. V et al. observed a cumulative incidence of 17% over 3 years.[48] Other data showed a variable estimated prevalence, from 0.16% in healthy patients to up to 64% among patients with intestinal bleeding.[50-52] These large variations are due to the different methodologies applied between studies.

In breast-feeding patients, most reactions are related to theLV, egg and soy in the maternal diet; however, wheat, corn, apple, fish, meat and sesame have also been described.[52,53] In formula-fed babies, milk and soy are the main causative agents, but extensively hydrolyzed formulas have been reported to cause proctocolitis in up to 10% of patients.[54]

Despite being a non-IgE-mediated reaction, studies indicate that about 40-50% of patients with Allergic proctocolitis present with atopy, and more than 60% of babies have a positive family history of allergy.[48,52,55]

Pathophysiology

The pathophysiological mechanism of allergic proctocolitis is not fully understood, but it is a non-IgE-mediated reaction.[6,22,56]

It is believed that the main related risk factors may be the immaturity of the innate and adaptive immune system, alteration of intestinal permeability, genetic susceptibility associated with sensitizing foods and dysbiosis.[57,58]

Sensitization to food antigens appears to play a key role in allergic proctocolitis, associated with a failure in the tolerance mechanism. Some studies have demonstrated the participation of several cells in the oral tolerance mechanism.[56,59] Pérez-Machado et al, in a study in children with allergies to multiple foods, demonstrated a failure in the production of TGF-β by regulatory cells in the small intestine.[60] One of the hypotheses for this deficit in the production of TGF-β by Th3 regulatory cells and for the impairment of the oral tolerance mechanism would be an ineffective response of innate immunity to the gut microbiota.[61]

Other studies suggest that a change in the composition of the gut microbiome may influence

immune tolerance by regulatory T cells (T-reg) and its homeostasis. Wang J. et al. demonstrated that these defects can compromise different pathways, including effector Treg cells, defect in the expression of CTLA4 and ICOS, and lower production of IL-10 by intestinal Treg cells.[58]

Another key cytokine in the intestinal inflammatory process would be TNF-α. Studies have already demonstrated its action on the tight-junctions of intestinal epithelial cells, thus altering the intestinal barrier and consequently leading to an increase in permeability.[62,63].

Histologically, biopsies of the rectum and large intestine of patients with proctocolitis showed eosinophilic inflammation in several layers.[48,56] Eosinophils are cells that involve both innate and adaptive immunity, due to their ability to interact with antigen-presenting cells and lymphocytes and to produce various mediators and cytokines.[56] Rycyck A et al. demonstrated an increase in EDN (eosinophil-derived neurotoxin) in feces, which could even represent a biomarker in this pathology.[64]

Despite theproctocolitis is a non-IgE-mediated allergy, some authors have shown sensitization to IgE in a minority group of patients.[65,66]

However, further studies are needed to better understand the pathogenesis and biomarkers of this pathology, which would allow better therapeutic guidance, assessment of prognosis and even of different types of allergic proctocolitis phenotypes.[65,67]

Diagnosis

The diagnosis of allergic proctocolitis, as well as non-IgE-mediated food allergies, is based on characteristic clinical history information. This is a generally eutrophic infant with adequate weight and height development and in excellent general condition, with blood-streaked stools with or without associated mucus.[13] Early diagnosis associated with adequate nutritional intervention will allow the baby to maintain its growth rate.

Symptoms appear, in most patients, gradually and persist until the food involved is removed.[13] If the patient has other gastrointestinal symptoms or changes in growth, an alternative diagnosis should be considered.[13]

Physical examination is usually normal, without lesions such as anal fissure, which often occurs in cases of constipation.

There is no definition in the literature of specific criteria for the diagnosis of allergic proctocolitis, however some data are useful for the elaboration of the clinical suspicion. These are[11](adapted from EAACI – European Academy of Allergy and Clinical Immunology):

– slight bleeding in the stool, hematochezia type, in an apparently healthy infant;
– resolution of symptoms after elimination of the allergen/food involved from the baby's or mother's diet, when exclusively breastfed;
– recurrence of symptoms after reintroduction of the food involved in the diet;
– exclusion of other causes of hematochezia.

Most patients who subsequently reintroduce food do not experience symptoms again, demonstrating the favorable course of proctocolitis with respect to immune tolerance. Some studies show that up to 20% of exclusively breastfed babies have spontaneous resolution of bleeding without changes in maternal diet, and that the long-term prognosis is excellent.[13,54,68] In view of this scenario, and in addition to the observation that episodes of rectal bleeding in childhood are mostly self-limiting, some authors have recently proposed to observe and wait for up to 4 weeks for spontaneous resolution, without an elimination diet, in exclusively breastfed infants, at very low risk of developing anemia.[56]

In the case of a period of more than one month, an elimination diet is suggested, and if the hematochezia resolves, an oral provocation test (OPT) should be performed. The oral provocation test should be performed after a short period of elimination diet, around 72-96 hours, to confirm the diagnosis.[11,56] There is no need, however, for it to be carried out in a supervised manner in a hospital environment. If TPO is positive, it is suggested to resume elimination diet for 3 months.[11,56]

Non-invasive exams

Laboratory tests, such as blood and stool analysis, including analysis of abnormal stool elements (EAF), stool parasitological examination (EPF), fecal alpha 1 antitrypsin assay, occult blood test, or human hemoglobin in stool, should not be used routinely for diagnostic confirmation of allergic proctocolitis.[13]

The blood count is usually normal, and some patients may have iron deficiency anemia.[13] Peripheral eosinophilia may be present in up to 43% of cases.[56]

Other inflammatory markers, such as elevated CRP and thrombocytosis, are usually absent.[56]

Fecal calprotectin levels are usually elevated when compared to healthy controls, indicating inflammation of the intestinal mucosa. However, its use in children under 1 year of age has restrictions due to the lack of validated normal values. This test is also not indicated to be routinely requested for the diagnosis of allergic proctocolitis, as there is no positive correlation between fecal calprotectin levels and positive provocation tests in patients with proctocolitis.[56]

Coproculture and screening for coccidia and viruses can be used to search for underlying infection.[56]

The use of allergy tests, such as prick test, patch test, and total serum IgE measurement have limited validity for diagnosis. Specific serum IgE measurement may be considered in breastfeeding patients who have associated IgE-mediated allergy symptoms, or in those with comorbidities such as atopic dermatitis, as well as before reintroduction of the implicated food after a long period of restriction.[56]

Ultrasound evaluation may reveal increased vascularization and thickening of the intestinal wall, especially the descending and sigmoid colon, suggesting the diagnosis. However, these findings are not specific to allergic proctocolitis, and inflammation in the rectum and sigmoid may not be visualized.

Invasive exams

Occasionally, the etiology of rectal bleeding may be of a different origin, and it is important for the differential diagnosis to exclude other pathologies through invasive tests, such as endoscopy, sigmoidoscopy, or colonoscopy.[56]

Endoscopic evaluation is not necessary for the diagnosis of allergic proctocolitis. Examination may reveal intestinal mucosal congestion, areas with petechiae, focal erythema, loss of vascular pattern, ulceration, diffuse nodularity, or, eventually, appear normal.[56]

Histological changes are characterized by eosinophilic infiltration of the intestinal mucosa and lamina propria, in addition to lymphoid hyperplasia.[56] The mucosal architecture is normally preserved and the eosinophilic infiltrate is typically concentrated in the rectum, especially in the epithelium and muscular layer of the mucosa. Because it is a non-uniformly distributed disease, multiple biopsies may be necessary.

Differential diagnosis of blood in stool

Digestive bleeding can manifest itself in several ways. Upper gastrointestinal bleeding occurs anywhere in the gastrointestinal tract proximal to the ligament of Treitz, which includes the esophagus, stomach, and duodenum. Lower gastrointestinal bleeding occurs in the small intestine (jejunum and ileum) and large intestine.[69]

The same can also be classified according to the characteristics of the stool: hematochezia corresponds to the passage of live blood through the rectum and usually represents lower digestive bleeding, although it can occur in upper digestive bleeding. Melena usually results from upper gastrointestinal bleeding and is characterized by black stools. Occult gastrointestinal bleeding is bleeding that is not visible to the naked eye and can cause symptoms such as iron deficiency anemia, pallor, or fatigue.[69]

The etiology of gastrointestinal bleeding in children varies with age, as can be seen in Table 2.

In addition to the diseases listed in Table 2, there are rarer causes such as malignancies, solitary rectal ulcer syndrome, typhlitis, incarcerated hernia or mesenteric thrombosis.[69]

The evaluation of the patient with bleeding in the stool should start with the anamnesis, highlighting the following points: duration and amount of blood, appearance of the stool and whether the blood appears to be mixed in the stool or just around it. Features such as general condition, abdominal pain, fever, weight loss, history of previous bleeding, use of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and other medications, in addition to underlying diseases such as liver disease or malignancy, should be investigated. Use of NSAIDs can cause ulcerations throughout the GI tract, including the small intestine and colon.[69] Also, some foods and medications, such as iron supplements, gelatin, and chocolate, can change stool color, mimicking melena or hematochezia.[70]

Acute hematochezia in a toxemic child with abdominal pain suggests intestinal ischemia as a complication of intussusception, volvulus, incarcerated hernia, or mesenteric thrombosis. In children under 2 years of age, intussusception should be the main suspect, and it may be associated with Meckel's diverticulum, polyp, lymphoid nodular hyperplasia, foreign body, lymphoma, among others.[69]

Colitis symptoms such as bloody diarrhea, tenesmus, nocturnal bowel movements, and abdominal

pain may arise in infectious or allergic colitis, in addition to necrotizing enterocolitis and Hirschprung's disease with enterocolitis.[69]

Because most infectious colitis is self-limiting and resolves spontaneously within two weeks, patients with bloody diarrhea for more than two weeks should be investigated for inflammatory bowel disease.[69]

Colitis does not always present with diarrhea. There is often blood mixed with normal stools. In children younger than 6 months, this finding suggests eosinophilic proctocolitis or lymphoid nodular hyperplasia. In infants between 6 months and 2 years it may also suggest juvenile polyp.[69]

When blood is not mixed with stool, there is likely to be perianal disease such as anal fissure or proctitis.[69] Also, when blood is mostly seen on toilet paper or in the toilet bowl after a bowel movement is complete, such a hypothesis is also more likely. If on physical examination there is a fissure and perianal erythema, a diagnosis of beta-hemolytic streptococcal cellulitis should be considered.[69]

Upon physical examination, the patient's hemodynamic status should be initially evaluated and peritonitis, signs of portal hypertension, and abdominal masses should be investigated.

Therapeutic approach

As with most food allergies, treatment of the Allergic proctocolitis consists of elimination of triggering antigens with a diet of exclusion of the suspected food. Cow's milk proteins are the most involved allergens.[71] However, occasionally the elimination of two foods together may be required, followed in this case by the exclusion of soy and egg.

For exclusively breastfed infants, elimination of food from the mother's diet results in resolution of symptoms in most cases, rarely requiring the use of formula to stop intestinal bleeding.[13] The exclusion of food from the maternal diet should always be accompanied by a nutritionist to assess the adequate supply of nutrients for the mother and baby, in addition to verifying the

Table 2
Etiology of gastrointestinal bleeding in children

Newborns	Breastfeeding infants	Preschoolers	School children and teenagers
Anorectal fissures	Anorectal fissures	Anorectal fissures	Anorectal fissures
Allergic colitis	Allergic colitis	Infectious colitis	Infectious colitis
Swallowed maternal blood	Infectious colitis	Intussusception	Henoch-Schonlein purple
Necrotizing enterocolitis	Intussusception	Meckel's Diverticulum	Meckel's Diverticulum
Volvo	Meckel's Diverticulum	Hemolytic uremic syndrome	Hemorrhoid
Hirschprung's Disease (toxic megacolon)	Hirschprung's Disease (toxic megacolon)	Henoch-Schonlein purple	Inflammatory bowel disease
Coagulopathies	Lymph node hyperplasia	Juvenile polyps	Juvenile polyps
Vascular malformations	Gastrointestinal duplication cyst		
Gastric and duodenal ulcer	Coagulopathies		
Neonatal transient eosinophilic colitis	Early-onset inflammatory bowel disease		
Gastrointestinal duplication cyst			

need for supplementation.[11] Breastfeeding should always be encouraged, and there is no indication to suspend breast milk supply.[56]

For babies who develop symptoms when fed infant formula, 80% respond to substitution with extensively hydrolyzed formula (FEH) and few cases require formula amino acid (FAA).[11,13,16] Soy protein-based formulas are generally not recommended as co-reactivity between cow's milk and soy proteins occurs in 10% to 30% of patients with proctocolitis.[1]

Removal of foods that cause Allergic proctocolitis, by exclusion in the maternal diet or in the formula-fed infant, results in rapid improvement of symptoms. In most cases, within 72 hours of dietary changes, resolution of hematochezia is observed, although stool bleeding may persist for up to 1 to 2 weeks for the most symptomatic patients.[11,16]

If, after 2 weeks of starting the exclusion diet, the infant is still symptomatic, it is important to check and adjust the exclusion of the antigen in the maternal diet and then check for other possible foods to be eliminated from the diet, suggesting the exclusion of soy, and later from the egg.[56,71] If more than one food protein is restricted from the diet of the breastfeeding mother, the importance of supervision by a nutritionist is again highlighted to ensure nutritional support and to avoid excessive maternal weight loss.[1,56]

The use of probiotics for the treatment of allergic proctocolitis still lacks more elaborate studies for its indication. A randomized clinical trial showed no benefit from using a probiotic, in addition to the maternal diet, in patients with proctocolitis.[16] Another study with very limited evidence suggests that the probiotic with Lactobacillus Rhamnosus GG may promote recovery or tolerance acquisition.[56]

Early and accurate diagnosis of allergic proctocolitis is important in order to avoid unnecessary exclusion diets that can have harmful health effects. Nutritional support is essential to avoid nutritional deficiency in the mother or in babies with allergic proctocolitis. Diet assessment by a nutritionist aims to provide food replacements that ensure adequate intake of vitamins and minerals, including mainly calcium, vitamin D, zinc and selenium. Supplementation of these nutrients is not always mandatory if there is an adequate diet.[1]

Prognosis and food reintroduction

The natural history of allergic proctocolitis is benign and most affected children outgrow this condition within the first year of life. Allergic proctocolitis rarely persists between the 1st and 2nd year of life.[22]

A prospective cohort, following 185 children with proctocolitis to assess possible factors associated with the development of tolerance, showed that 99.4% of patients acquired tolerance at a median age of 11 months (10 to 13 months). However, in a group of 57 children, 33% were only able to ingest the offending food between 12 and 19 months. The main factors related to this acquisition of "delayed tolerance" were: delay in the introduction of complementary foods, concomitant atopic dermatitis, familial atopy, and ingestion of infant formula milk (at least once).[67]

In the study by Martin VM et al., following 153 patients diagnosed with allergic proctocolitis, it was observed that the average age for successful reintroduction of the causative food was around 11 months. In this study, 15% of the patients did not have any dietary restrictions and, despite continued exposure to the food, developed tolerance to the foods involved throughout childhood, however, some of these at a later age.[48]

Despite its benign character and complete resolution, one study suggests that proctocolitis could be a risk factor for the development of functional gastrointestinal disorders (FGID) in later childhood. FGID is characterized by intestinal motility disorder and visceral hypersensitivity (irritable bowel syndrome). The longer duration of hematochezia would be the main factor associated with the presence of these symptoms at four years of age.[72]

Although classically non-IgE-mediated, some cases of proctocolitis may present with IgE specific to the causal food, or develop IgE-mediated symptoms later in life, especially in children who have concomitant atopic dermatitis. For this reason, although it is not recommended to measure food-specific IgE in most cases of proctocolitis, the EAACI (European Academy of Allergy and Clinical Immunology) recommends that specific IgE should be measured in children with associated atopic dermatitis. before reintroduction of the causal food, after long periods of exclusion.[22]

Based on this aspect, a recent study by Cetinkayan et al. suggests that there could be three phenotypes of proctocolitis, according to the presence or development of IgE specific to the suspected food. There is a phenotype without IgE sensitization for the food in question, a second phenotype with IgE sensitization, but without the presence of IgE-mediated symptoms,

another with positive specific IgE and evolution to the IgE-mediated clinical form. The authors observed that individuals with the "transition to IgE-mediated form" phenotype would reach tolerance later than the other two forms. These findings, however, need to be confirmed by further studies.[65]

As it is benign and self-limiting, the food reintroduction of the suspected food can be conducted at home, gradually, under the guidance of the doctor, when he considers that the child has probably already reached tolerance, which usually occurs up to 11-12 months of age for most patients.[1,22,48]

If the diagnosis was not so accurate and the presence of blood in the stool was mild, reintroduction of food can be attempted earlier, given the transient nature of the disease.[1] Some authors also suggest that the early introduction of other foods, starting at 4 and a half months, could accelerate the development of milk tolerance in children with allergic proctocolitis.[48]

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