

REVIEW ARTICLE

Food Protein Induced Proctocolitis: A Benign Condition with an Obscure Immunologic Mechanism

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ARTICLE HISTORY

Received: October 26, 2016

Revised: March 05, 2017

Accepted: March 08, 2017

DOI:

10.2174/1871530316666170331165356

Abstract: Food protein-induced proctocolitis (FPIP) is the most common colonic manifestation of food allergy in infants, accounting for up to 60% of exclusively breast-fed children. The causative foods derived from the mother's diet, which are then excreted in her milk. The suggested risk factors for the development of FPIP are an immature immune system, altered intestinal permeability and other factors that activate local immune function, such as genetic susceptibility in combination with particularly sensitizing foods. FPIP is an enhanced immune responsiveness of some infants to very small amounts of food antigens, inducing an inflammatory mucosal response, mediated by T cells.

Keywords: Breast feeding, food allergy, infants, immunologic response, intolerance, allergic proctocolitis.

INTRODUCTION

Although breast-fed infants appear to have a lower incidence of allergic reactions to food proteins than formula-fed infants, approximately 0.5 to 1% of exclusively breast-fed infants can develop allergic reactions, such as food protein-induced proctocolitis (FPIP) [1]. FPIP, formerly known as allergic or eosinophilic proctocolitis or protein intolerance, causes rectal bleeding in otherwise healthy young infants which, in most cases, resolved by late infancy. The mechanism has been suggested to be a non-immunoglobulin E (IgE) mediated inflammation of the distal colon and rectum in response to one or more food proteins [2, 3]. Purported causative foods include cow's milk, soy, fish, egg and wheat. Because approximately 60% of all cases of FPIP are found in exclusively breast-fed children [4, 5], it is highly likely that the causative allergenic proteins derived from the mother's diet which are then excreted in her milk (Fig. 1). Consequently, an *elimination diet* of the lactating mother for a period of 2 up to 4 weeks is often used for the diagnosis and treatment of FPIP [6].

The FPIP pathophysiological mechanism has not been fully identified. The data is scarce. This review will focus on the indicative causative proteins and the immune mechanisms

of the food intolerance responsible for causing the mucosal inflammation underlying FPIP.

PROTEINS INVOLVED IN FPIP

FPIP is characterized by inflammatory alterations of the colon and rectum secondary to an immune reaction triggered by the ingestion of foreign proteins [7]. Certain foods have been implicated in FPIP. Namely, in a published series of 95 breastfed infants with bloody stools, 65% were determined to be attributable to maternal ingestion of cow's milk, white egg, corn and soy ingestion in 19%, 6%, and 3% of the cases respectively [8]. A study of 60 infants with FPIP revealed that 3.3% of patients had multiple food allergy [9].

Cow's milk proteins are excreted in breast milk after the ingestion of dairy products by the mother. Kilshaw & Cant demonstrated that the beta-lactoglobulin of cow's milk may be detected in samples of human milk between four and six hours after the mother has ingested cow's milk [10]. Cow's milk contains more than twenty five different proteins, but only whey proteins: α -lactalbumin, β -lactoglobulin, bovine serum albumin, and lactoferrin, as well as the four caseins, have been identified as allergens [4]. The most allergenic protein is β -lactoglobulin. Sorva *et al.* [11], showed that β -lactoglobulin in human milk may contribute, but does not alone explain the development of cow's milk allergy in breast-fed infants. The most relevant finding was the detection of the intact bovine α -S1-casein in both term and pre-term colostrum. According to study results of Orru *et al.* [12], bovine α -S1-casein, a major cow's milk allergen, is

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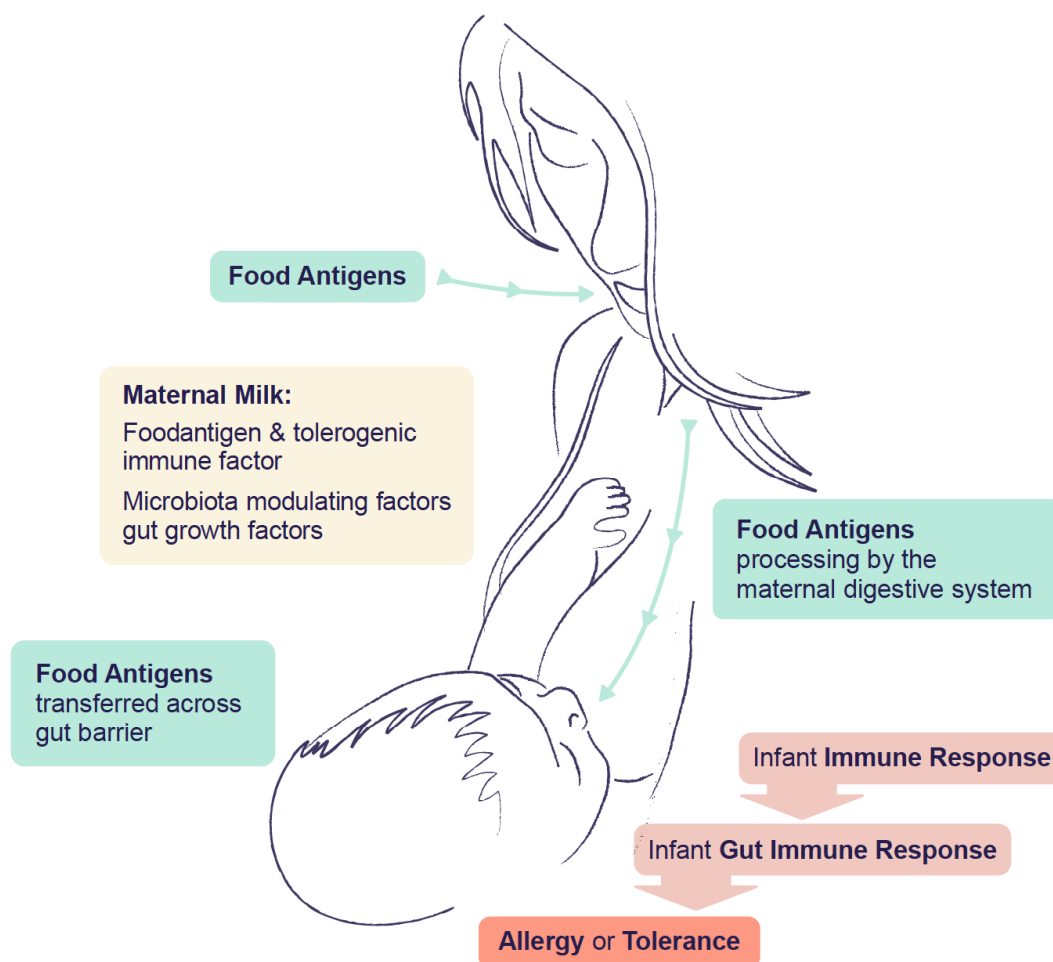


Fig. (1). The development of hypersensitivity or tolerance to food antigens in breast-fed infants. In FPIP, food causative allergenic proteins, carried *via* breast milk can sensitize exclusively breast-fed infant and then trigger a T-lymphocyte mediated allergen specific immune response.

readily secreted in human milk, and so could be considered a possible cause of sensitization in exclusively breastfed infants. The rest of affected proteins correspond to infants fed formulas containing cow's milk proteins or soy [7]. Odze *et al.*, reported that up to 30% of all patients with FPIP are allergic to both proteins, cow's milk proteins and soy [13]? In a clinical overview, where 95 exclusively breast-fed infants had been evaluated during the past 20 years, the causative protein could not be identified in 11.6% of patients [14]. In this study group, L-amino acid formula was befitting for 4.2 % of patients [14]. Furthermore, gastrointestinal allergic reactions, in patients with persistent symptoms of FPIP, are more likely to be triggered by residual peptides in extensively hydrolyzed formula (eHF) because T-cell epitopes are typically smaller than B-cell, (IgE-binding) binding epitopes [15]. Hence, these patients represent a group for whom amino acid formula (AAF) might be essential [16].

IMMUNE MECHANISMS

Food proteins carried *via* breast milk can sensitize exclusively breast-fed infant, and then trigger a T lymphocyte mediated allergen-specific immune response (Fig. 1) [17].

Specifically, human milk contains viable leukocytes that may play a role in antigen processing and presentation to neonatal lymphocytes in the intestine [18, 19]. The development of hypersensitivity to food antigens may not depend on the amount of antigen, but rather on the enhanced immune responsiveness of some infants to very small amounts of antigen. Hence, the development of FPIP depends on certain factors (Table 1).

Table 1. Proposed immunologic mechanisms of food protein induced proctocolitis.

Immaturity of the gut
High infiltration of eosinophils
Antigen specificity
Strong genetic influence
Increased expression of secretory immunity
Delayed maturation of intestinal microbiota

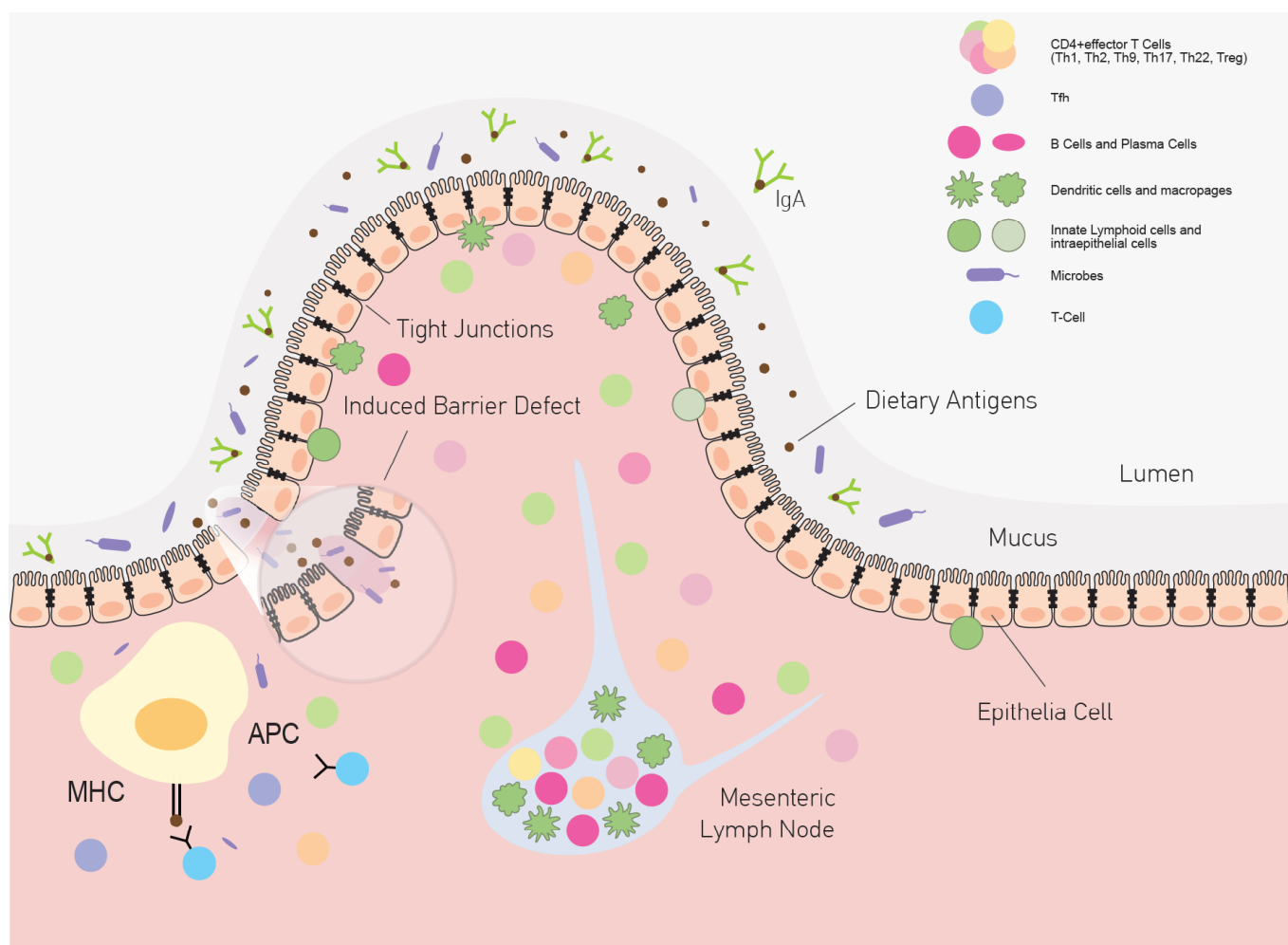


Fig. (2). Schematic representation of the intestinal mucosal immune system and laminal environmental factors. IgA binds to food antigens in the mucus layer, where it neutralizes them and prevents them from penetrating the epithelium. However, free antigens can also be transferred passively across gut barrier with less efficiency. Then antigen will be probably picked up by infant antigen presenting cell (APC) that will induce the generation of regulatory T cells. A marked eosinophilic infiltration (characteristic in FPIP) may significantly alter tight junctions and collectively may lead to increased intestinal permeability to food proteins.

Immaturity of the Gut

After birth the gut mucosa is challenged by a myriad of antigens, from viruses to commensal microbiota and dietary antigens. Although controlled in the mature gut, these antigens may induce inflammation in the developing gastrointestinal tract [20]. In particular, both intracellular and paracellular transport of macromolecules through epithelium is increased in infants [21]. Additionally, an altered barrier function of the gut epithelium, including a developmental immaturity of the components of the gut barrier in early childhood, might account for the increased prevalence of food allergy in infancy. Bone *et al.* suggested both intestinal immaturity and marked eosinophilic infiltration, which may significantly alter tight junctions, lead to increased intestinal permeability to food proteins [7]. Furthermore, insufficient secretion of digestive enzymes causes reduced digestion and increases the amounts of undigested proteins in the intestinal lumen. Besides, infants often have gastrointestinal infections, which damage the epithelium and allow permeation of proteins into the lamina propria [22].

On the other hand, secretory-IgA (s-IgA) is the most plentiful immunoglobulin on mucosal surfaces and constitutes a first line defense antibody in protecting the intestinal epithelium. It binds to antigens in the mucus layer, where it neutralizes harmless food antigens and prevents them from penetrating the epithelium [23]. However, macromolecules do cross the gut epithelium and can be recognized by the immune system (Fig. 2). Furthermore, Kukkonen *et al.* showed that high intestinal IgA in early life is associated with minimal intestinal inflammation and indicates reduced risk for IgE-associated allergic diseases [24]. Nevertheless, in the newborn period, there is a tendency of the immature intestines of the neonates to allow excessive uptake of foreign antigens across the mucosal barrier [25]. Additionally, a lack of IgA in milk may lead to an increased exposure of the intestinal mucosa to potential allergens and enhance the risk of food allergies [26]. This is even indicated by the aspect that the higher concentration of IgA in human milk in the first couple of weeks of lactation may explain why the majority of infants with cow's milk allergy did not show symp-

toms suggestive of cow's milk allergy until an age of 2 to 4 weeks [26].

The Role of the Eosinophils

It is thought today that eosinophils may be directly responsible for tissue injury in allergic colitis and it is interesting to note that these cells can bind IgA, which are normally present in breast milk, and undergo degranulation [8]. Furthermore, eosinophils are often clustered in proximity to the lymphoid aggregate below epithelial erosion. This suggests their role in response to antigen uptake and the possible site of T-cell interaction [14]. The immature immune system fails to prevent the infiltration of eosinophils, leading to the destruction of epithelial cells, which are responsible for clinical features [27]. Subsequently, eosinophil-derived mediators can stimulate a secretory response from epithelial cells *in vitro*. This may represent an important pathway in the development of diarrhea, a symptom which may be present in patients with FPIP [27].

Antigen Specificity

Antigen specificity is one concern, as certain infants with FPIP exhibit oligoclonal, but not monoclonal, antigen-specific reactions against food proteins, even though they have not been exposed to food antigens other than those in breast or formula milk during early infancy [28]. Feeding cow's milk during the first three days of life stimulates IgG antibody production to cow's milk proteins, which was still detectable at 2 years of age. This antibody production confirms that early feeding can be critical for the development of immune responses to food antigens and sensitization [29]. Early short-term exposure to cow's milk formula seems to have more importance for the development of immune response to cow's milk proteins than feeding cow's milk formula later in life [29].

Furthermore, evidence has been revealed that in a small percentage of patients, FPIP is actually caused in an antigen specific manner. In support of this notion, Ohtsuka *et al.* reported 2 infants who had bloody stool on the first day of life, before initial feeding, but subsequently never developed bloody stool even with breast milk without maternal diet modification [30]. These facts suggest that there are some special enteral environments in early infancy that may result in antigen-nonspecific hemorrhage in the colon. Thus, a certain proportion of FPIP patients may have antigen-nonspecific bloody stool, but in order to discuss FPIP, we must include these patients because very few studies other than Lake have confirmed the antigen specificity in their subjects by oral food challenge [14].

The Predominant Genetic Influence

It has been suggested that an allergic reaction in the first weeks of life could be due to an intrauterine sensitization, secondary to transplacental antigen passage [31]. However, recent studies revealed that total IgE and allergen-specific IgE in cord blood does not reflect sensitization in utero, but seems to be the result of materno-fetal transfer of IgE. This challenges the concept of intrauterine sensitization and thereby the rationale behind allergen avoidance during preg-

nancy [32, 33]. Additionally, infants who receive exclusive natural breastfeeding and present with a genetic predisposition towards allergies, may also show symptoms of allergic colitis [34]. Currently, it is generally recognized that there is a genetic predisposition towards allergy that acts in association with one or more triggers [35]. In a recent study, Kaya *et al.* described 60 infants with FPIP and found that 6.7% were siblings [9]. Although rare, FPIP in first-degree relatives of patients had been reported earlier. Fagundes-Neto and Ganc described five infants, who were cousins from two distinct family groups, with FPIP [34]. Hence, it is estimated that genetic factors might exert a fundamental role in the expression of this allergic disease, since a high occurrence in atopic family history in children with eosinophilic colitis has been described. This occurrence shows us the need to investigate the genetic component of the disease.

Increased Expression of Secretory Immunity

The results from a recent retrospective analysis, after an RT-PCR analysis of mucosal histological findings of patients with FPIP, demonstrated that the enhanced IL-6, chemokine CCL11 and CXCL13 expression in the mucosa is of major importance [28]. In detail, CXCL13 is involved in attracting B cells into developing lymphoid tissue [36], which is considered the dominant characteristic in FPIP. In particular, enhanced CXCL13 and CXCR5 (receptor for CXCL13) expression observed in neonates with PFIF is convenient for IgA synthesis. This is revealed by an immunohistochemical analysis, which showed an infiltration by IgA-bearing cells, possibly suggesting that the enhanced immunological reaction is against food antigens [28].

Additionally, transforming growth factor (TGF)- β , which is present in breast milk, stimulates further antigen-specific IgA synthesis. Hence, it is possible that the enhanced CXCL13 expression and the TGF- β in breast milk stimulate the lymphoid follicle formation and induce lymphoid hyperplasia, leading to rectal bleeding [28].

Furthermore, in the breast-fed infant, it is tempting to suggest that the maternal dietary protein is complexed in some fashion with breast milk immunoglobulin IgA or another immunologic component that is only cleaved from the protein antigen by some environmental feature of the recto-sigmoid, such as microbial IgA proteases. The prominent role of the lymphoid nodules in the lower colon of antigen sampling suggests that this may be the site of initiation of the inflammatory response, substantiating the specific location of FPIP onset [14].

The Role of the T-Cells

Food proteins carried *via* breast milk can sensitize exclusively breastfed infants and then trigger a T lymphocyte-mediated allergen specific immune response. Delayed type hypersensitivity reaction has been proposed as a pathogenetic mechanism of allergic proctocolitis by Dargent JL *et al.* [37]. Along these lines, Morita H *et al.* detected, by analyzing 89 blood samples collected from infants all over Japan, that antigen-specific T-cell responses in patients with non-IgE-mediated gastrointestinal food allergy, including FPIP, are predominantly skewed to Th2 [38]. The same group also

reported that the concentrations of 3 Th2 cytokines, IL-3, IL-5, and IL-13 were found statistically significant and much higher for the above patients.

In an exploratory study, Cseh A *et al.* revealed that infants with persistent symptoms of FPIP presented with low numbers of regulatory T cells (Tregs), a decreased prevalence of activated T-cells and a shift to Th2 direction in balance compared with controls [39].

Delayed Maturation of the Intestinal Microbiota

There is evidence that gut microbiota modulates mucosal physiology, barrier function, and systemic immunological and inflammatory responses [40]. In normal newborn babies, there is transient intestinal colonization by facultative anaerobes immediately after birth. Thereafter, obligate anaerobes such as *Bifidobacterium*, *Bacteroides*, *Clostridium* and *Lactobacillus* species increase and establish colonization, with reduction of facultative anaerobe counts [41]. However, the counts of obligate anaerobes were significantly lower in the feces of the exclusively breastfed infants with blood-streaked stools than in healthy breast-fed infants [20, 42]. This deficiency might be one of the factors which play a role in allergic proctocolitis.

These findings suggest that there is delayed maturation of the intestinal microbiota flora in patients with FPIP. In addition, Atarashi *et al.* revealed that a mixture of 46 strains of *Clostridium spp.*, including *C. leptum* and *C. coccoides*, promote regulatory T-cell (Treg cells) accumulation and also affect their function in the colon of mice [43]. The fact that there are lower counts of *C. leptum* and *C. coccoides* in the feces of patients with FPIP suggests that impaired induction of Treg cells in the colon may be involved in the pathogenesis of FPIP [43]. Moreover, *C. leptum* and *C. coccoides* also promote accumulation of IgA-positive cells in the colon [44] and induce IgA production through induction of Treg cells that produce TGF- β [45]. In support of this, sIgA concentrations in the feces tend to be lower in patients with FPIP than in control subjects [46]. These findings suggest that impaired induction of Treg cells and IgA, which contribute to homeostasis in the intestine, due to delayed maturation of the intestinal microbiota, may have a causative association with FPIP.

CONCLUSION

The gastrointestinal mucosal immune system must constantly analyze antigenic information and respond appropriately to pathogens, commensals, and food antigens. Hence, the ability of a dietary protein to be transported antigenically intact in human breast milk and subsequently the development of hypersensitivity to food antigens may not depend on the amount of antigen for the onset of FPIP. It is rather an enhanced immune responsiveness of some infants to very small amounts of food antigens, as cow's milk, soya, egg, rice and wheat although a substantial proportion of food triggers is not identified. These food proteins induce an inflammatory response, in an antigen specific manner, apparently limited only to the lower colon, likely due to the prominent role of the lymphoid nodules. Subsequently, the increased expression of secretory immunity and the TGF- β in breast

milk stimulate the lymphoid follicle formation and induce lymphoid hyperplasia, leading to rectal bleeding. Hence, the altered immune response results in a reduction in intestinal immune suppressor/tolerance. In this regard, advances in our understanding of the complexities of the underlying mechanisms may provide direction for future research pertaining to the pathogenesis of FPIP.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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