

Food allergy and constipation in childhood: how functional is it?

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An increasing incidence of food allergy, especially to cow's milk proteins, is observed in children living in the industrialized regions of the world. In some cases responding to an evicton diet excluding offending foods, the 'functional' constipation can be caused by inflammation of the intestinal wall infiltrated by eosinophils. Understanding the complex mechanisms involved could help to improve the management of idiopathic functional constipation in children by addressing the aetiology instead of treating the symptoms. *Eur J Gastroenterol Hepatol* 18:125–128 © 2006 Lippincott Williams & Wilkins.

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Introduction

Even in young children, at least in the industrialized world, functional constipation is becoming increasingly frequent. Changes in the way of living and low-residue diets are most probably the causes responsible.

Allergic diseases have also become increasingly frequent, especially food allergy. Environmental causes, such as greater hygiene and food processing seem to be responsible.

The overconsumption of cow's milk leading to constipation is well documented. However, in some instances, 'functional constipation' is not caused by high intakes of milk but an allergic-type effect responding favourably to the evicton diet of allergenic foods, especially cow's milk proteins.

Mechanisms relating constipation to allergy are dysmotility and changes in the mucus composition caused by inflammation of the rectal wall by an eosinophilic infiltration. A similar phenomenon of dysmotility caused by inflammation and eosinophilic infiltration can be observed in eosinophilic esophagitis.

The average prevalence of constipation increases exponentially from childhood to adulthood when it becomes one of the most frequent complaints in the gastroenterology outpatient clinic. In the industrialized regions of the world, constipation is also responsible for the use of many drugs sold over the counter as automedication. In paediatrics, infants are more prone to loose stools than to constipation, and it is surprising to observe how often mothers or caregivers tend to report the minimal details about the bowel habits and quality of stools of their

infants in contrast with their almost total ignorance of the bowel habits of their older children of school age.

In the great majority of cases, paediatricians deal with 'functional' constipation, a symptom and not a specific disease. Maturation of the sphincters, psychological and environmental factors, and diet errors are among the many well-known factors that influence bowel habits. Is allergy one of them? What are the possible mechanisms involved?

Epidemiology of functional constipation in children of industrialized regions

In 1976 constipation represented 3% of the office consultations in general paediatrics and as much as 25% of specialized paediatric gastroenterology consultations [1]. However, the real prevalence of constipation is hard to determine precisely because the definitions may vary, and the majority of cases are managed by the family doctor, the pharmacist or herbalists....

An Italian study involving children below the age of 12 years and using the Rome criteria [2], conducted in primary healthcare centres for routine prevention, reported that 0.7% of all children attending these centres presented with functional constipation.

In a recent review of more than 4000 charts of children younger than 2 years, the prevalence rate for constipation was 2.9% in the first year of life and 10.1% in the second year of life; functional constipation was the cause in 97% of children [3].

The natural history of constipation in young children has been poorly studied. Follow-up 3–12 years after the initial

evaluation and treatment of constipation showed a better recovery rate when the children were treated before the age of 2 years than in children aged between 2 and 4 years, but chronic constipation persisted in a third of patients [4].

Epidemiology of food allergy and its causes

Cow's milk protein allergy (CMPA) affects approximately 2–3% of infants under 2 years of age, and symptoms suggestive of CMPA are observed in approximately 5–15% of infants. Reproducible clinical reactions to cow's milk proteins in human milk have been reported in approximately 0.5% of breastfed infants [5]. In childhood, food allergy remains an important health problem: approximately 2.1% of children report symptoms of food allergy and asthma or allergic rhinitis, 1.9% are sensitized to food allergens and 0.1% have positive skin prick tests for food allergy [6]. In a cross-sectional descriptive questionnaire-based survey conducted among French school children [7], the clinical signs of food allergies were digestive in one third of patients; the main foods reported as causing adverse reactions were cow's milk (11.9%), eggs (9.4%), kiwis (9.0%), peanuts (8.2%), fish (7.8%), tree nuts (7.8%), and shrimp (5.3%).

A number of epidemiological studies have suggested that the increase in the prevalence of allergic disorders that has occurred over the past few decades [8] is attributable to a reduced microbial burden during childhood. However, the mechanisms linking the reduced exposure of children to pathogenic and non-pathogenic microbes to enhanced responses of T helper type 2 cells are still controversial [9,10]. In addition to improved hygienic standards in the past few decades, social changes, including the availability of functional food and food enriched in antioxidants, may have increased the prevalence of atopic diseases in the western world [11]. The issue of the allergenicity of particular foods is highly complex, and with our current knowledge we have just begun to understand some of the contributions of industrial processing to the allergenic properties of proteins and foods [12].

Constipation is a symptom, not a disease

It is usual to state that up to 95% of cases of constipation have no organic origin and are not caused by an underlying structural, metabolic or endocrine disease. Most often the assessment of the patient as a whole, paying attention to psychological and nutritional factors, is guided only by a detailed history and some investigations of the anorectal motor and sensory functions, but seldom addresses the many physiopathological mechanisms of constipation. In paediatrics, the main preventive factors against constipation seem to be simply water and vegetable consumption and training on the use of the toilet at school [13].

Nevertheless, in some cases, 'functional' constipation resists all treatments, and experts have recognized the limits of our knowledge. They recommend investigating the role of constitutional factors of the intestine [14], including the quality of muscular structures, the autonomic nervous system and messengers (hormones, neuropeptides and receptors), the efficacy of intestinal motility and sensitivity, the visco-elasticity of the intestinal wall, and the secretory properties of the mucosa and its ability to absorb water, bile salts and ions.

Constipation as a symptom of food allergy

The clinical spectrum of food allergy ranges from immediate-type reactions such as urticaria and angioedema, vomiting and diarrhoea to intermediate and late-onset reactions, including atopic dermatitis, infantile colic, gastro-oesophageal reflux, chronic diarrhoea and constipation. The association of constipation caused by the excessive consumption of cow's milk is well documented [15] and CMPA has been recognized as an underestimated cause of constipation since 1978 [16].

In an open study published in 1995, Iacono *et al.* [17] hypothesized that intolerance to cow's milk can also cause severe perianal lesions, with pain on defecation and consequent constipation in young children. The authors also reported proctitis with monocytic infiltration in two patients cured with a cow's milk protein-free diet [17]. Later, in a clinical randomized, controlled trial the authors showed inflammation of the rectal mucosa responding to a soy milk substitution diet in 37% of patients [18]. Others have also described chronic refractory constipated children with CMPA along with allergic rectitis [19] or colonic lymphoid nodular hyperplasia and mildly increased eosinophil density [20].

Mechanisms relating allergy to constipation

The diversity of food allergy manifestations and the complexity of the different immunological mechanisms do not permit an automatic interpretation as a symptom of allergy of any dysmotility manifestation responding to an exclusion diet [21]. Recent advances in the understanding of the pathophysiology of allergy and immunological mechanisms show that, apart from IgE-mediated atopic manifestations or T-cell-mediated reactions, non-IgE-mediated or T-cell-mediated allergic gastrointestinal disorders also exist and are implicated in dietary protein enteropathy, protein-induced enterocolitis, and proctitis. There are no well-established tests available, but skin prick tests and food-specific serum IgE and IgG4 antibodies may help in identifying the offending foods. Eviction and blind challenges remain the main diagnostic tools, but are not easy to perform. Another approach consists of the measurement of eosinophil markers in stool or serum samples [22,23]. Faecal eosinophil cationic protein, for immediate-type reactions, and TNF- α , for

delayed-type reactions, could distinctly indicate various reaction types of food allergy [24].

Motility

The same symptoms, responding to food eviction, are present in irritable bowel syndrome and support the aetiopathological role of food [25].

An anal spasm rather than colonic dysmotility is an explanation for the mechanism of constipation related to cow's milk allergy [26]. In the cases reported by Iacono *et al.* in the article published in this edition (pp. 143–150), constipation is the selecting symptom and anal tone is increased whereas the rectal sensitivity threshold is decreased as expected in cases of rectitis. The description of endoscopic lesions (erythematous friable mucosa without erosion) and histological findings (intra-epithelial lymphocytes and eosinophils and lamina propria infiltration by eosinophils decreasing after an elimination diet) corresponds to a rectal inflammation. The presence of immune or inflammatory cells is observed in the epithelium and the submucosa, but also at deeper levels of the gastrointestinal wall such as the circular or longitudinal muscular layers. In inflammatory conditions, smooth muscles are not only targets for inflammatory mediators but are also a source of cytokines and inflammatory mediators [27].

Eosinophils

Eosinophils are bone-marrow-derived granulocytes that are involved in both allergic and non-allergic inflammation. They possess a diverse repertoire of functional responses and effector capabilities, including the release of preformed cytotoxic granule proteins, superoxide production, leukotriene biosynthesis and cytokine production. In healthy conditions, most eosinophils reside in the lamina propria in the stomach and intestine. Eosinophil homing to these sites occurs during embryonic development and eosinophil localization to the lamina propria is critically regulated by eotaxin, a chemokine constitutively expressed throughout the gastrointestinal tract except in the oesophagus, where its expression is not sufficient for eosinophilic accumulation, this organ being devoid of eosinophils at baseline [28]. Eosinophils also play a role in several inflammatory conditions, such as intestinal infections, hypersensitivity reactions, primary eosinophilic inflammations and several other chronic intestinal disorders. Depending on the responsible trigger, their effects may be beneficial or detrimental. There is increasing evidence that, as with the findings in the skin and lung, mast cells and recruited eosinophils by chemokine eotaxin are key cells in the development of dysmotility in allergic diseases and other inflammatory conditions, and that they mediate their action through the release of very potent granule constituents [29]. The action of histamine on the enteric nervous system and the

different neuronal selective receptors in humans is not yet fully understood [30]. Electron microscopy has shown eosinophils in the vicinity of damaged axons, indicating that eosinophils mediate a pathological response [31].

Is it possible to compare the symptoms of retention with eosinophilic infiltration and allergy occurring in the anorectal region and a similar situation occurring in eosinophilic oesophagitis? In eosinophilic oesophagitis, characterized by pain and impaction of food, dysmotility is also associated with eosinophilic infiltration. A few manometric abnormalities such as spasms have been described in the rare motility studies on eosinophilic oesophagitis. It is also hypothesized that activation of acetylcholine by histamine may cause contraction of the muscle fibres in the muscularis mucosae, resulting in the formation of the typical endoscopic oesophageal rings [32]. On the other hand, rare cases of eosinophilic muscular infiltration have been reported in the literature on achalasia [33,34]. Statistically significant differences were found between patients with eosinophilic oesophagitis and controls for mean values for the thickness of combined mucosa, submucosa and muscularis propria [35]. The same could be possible at the level of the inflamed anal and rectal walls, with some consequences on their biomechanical properties.

Mucus

Mucus protects the mucosa against mechanical and chemical aggressions.

In an experimental model in rats with loperamide-induced constipation, the mucus production of crypt epithelial cells was reduced as was the mucus thickness at the level of the mucosal and faecal surfaces [36]. This phenomenon could change the viscoelasticity of the faeces, one of the parameters that play an important role in the quality of defecation. In the study by Iacono *et al.* [37] the reduction in the production of mucus as a consequence of an allergic reaction contradicted the findings reported in asthma, although goblet cell density can be diminished in cases of allergic conjunctivitis in humans [38]. In mice, the repetitive application of allergens in the conjunctiva induced a reduction in the number of filled goblet cells [39].

Conclusion

Stressing the role of allergy to cow's milk proteins (and perhaps to other food products) as a possible cause of constipation allows, at least in selected cases, the prescription of a rational aetiological treatment of 'functional' constipation instead of the systematic use of laxatives or of the too often inefficient recommendation of a high-residue diet. It may provide a newer, less simplistic and mechanistic approach to the pathophysiology of 'functional' constipation.

The promotion of research in the field of inflammation and its consequences on the neuromuscular and secretory systems could open a new area for more targeted treatments addressing eosinophilic infiltration.

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