

Educational Clinical Case Series

Allergic gastrointestinal motility disorders in infancy and early childhood

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Pediatr Allergy Immunol 2008; 19: 383–391.

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Gastro-oesophageal reflux disease, constipation and colic are among the most common disorders in infancy and early childhood. In at least a subset of infants with these functional disorders, improvement after dietary elimination of specific food proteins has been demonstrated. Gastrointestinal food allergy should therefore be considered in the differential diagnosis of infants presenting with persistent regurgitation, constipation or irritable behaviour, particularly if conventional treatment has not been beneficial. The diagnosis of food protein-induced gastrointestinal motility disorders is hampered by the absence of specific clinical features or useful laboratory markers. Gastrointestinal biopsies before commencing a hypoallergenic diet may provide the most important diagnostic clues. Early recognition is essential for the optimal management of these patients to prevent nutritional sequelae or aversive feeding behaviours. Treatment relies on hypoallergenic formulae, as well as maternal elimination diets in breast-fed infants. Further research is required to better define the pathological mechanisms and diagnostic markers of paediatric allergic gastrointestinal motility disorders. The following article will present three instructive cases followed by discussion of the clinical presentation, diagnosis, treatment and natural history of food allergic motility disorders in infancy and early childhood.

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Key words: colic; constipation; food allergy; gastro-oesophageal reflux; infant; motility

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Accepted 19 June 2008

Gastro-oesophageal reflux disease (GORD), constipation and colic are among the most common disorders in infancy and early childhood. In at least a subset of infants with these functional disorders, improvement after dietary elimination of specific food proteins has been demonstrated (1, 2). Gastrointestinal food allergy should therefore be considered in the differential diagnosis of infants presenting with persistent regurgitation, constipation or irritable behaviour, particularly if conventional treatment has not been beneficial.

Gastrointestinal symptoms, including vomiting and diarrhoea, occur in both immediate and delayed-onset allergic reactions (3). In immunoglobulin E (IgE)-mediated reactions, acute

vomiting and diarrhoea are motility events that aid in the elimination of the offending food from the gastrointestinal tract, often within minutes of ingestion (2). By contrast, the non-IgE-mediated gastrointestinal manifestations occur up to 48 h after ingestion. These reactions typically include persistent regurgitation/vomiting, chronic diarrhoea, poor feeding and may result in failure to thrive (4). As no single diagnostic test for non-IgE-mediated food allergy is currently available, the diagnosis still relies on clinical improvement after antigen elimination and relapse upon challenge. In addition, gastrointestinal biopsies may provide important diagnostic clues.

Our understanding of the exact mechanisms leading to motility disturbances during allergic

reactions is limited (5). Gastrointestinal peristalsis is controlled by a complex neuronal network, the enteric nervous system (ENS). Recent studies have demonstrated direct interaction of mast cells, and possibly eosinophils and lymphocytes, with submucosal nerve fibres (6). In addition, increased intestinal and colonic contractility during food challenge has been shown in animal models of anaphylaxis (7). It therefore appears plausible that release of mast cells mediators, T helper 2-type cytokines and other neurotoxic compounds as a result of food allergic reactions may affect the ENS and cause peristaltic dysfunction (8, 9). Furthermore, stimulation of afferent nerve circuits via the brainstem may trigger transient lower oesophageal sphincter relaxation (TLOS) or activation of the emetic reflex (10).

The following article will present three instructive cases followed by discussion of the clinical presentation, diagnosis, treatment and natural history of food allergic motility disorders in infants and young children.

Case 1

A 4-month-old girl is referred to the gastroenterology clinic because of persistent frequent regurgitation, poor feeding and slow weight gain. She was delivered via elective Caesarean section at 38-wk gestation after an uneventful pregnancy. Her birth weight was 3.0 kg, and her length 48 cm, both corresponding with the 25th growth percentiles. Breast feeding was established on day 2, and supplemental cow's milk formula was given while her mother recovered post-operatively. In the first weeks of life the girl was feeding well, although her parents noticed increasing regurgitation of 20–40 ml of breast milk after most feeds. There was no associated diarrhoea. At 4 wk of age, the parents sought the advice of their maternal and child health nurse who reassured them as the infant was thriving and generally well. However, at the 2-month check-up the weight gain had slowed, with a drop to the 10th percentile, while linear growth had continued along the 25th percentile. Because of the decrease in growth velocity and large volume regurgitation, the parents commenced supplemental cow's milk formula. The infant initially achieved some catch-up growth to the 25th weight percentile. At 3 months of age the infant was weaned completely onto formula as her mother wished to return to work. The type of formula was changed from standard to a casein-predominant 'anti-regurgitation' formula.

Despite this, the regurgitation increased noticeably over the following weeks, both in volume and frequency. When reviewed by a paediatrician at 4 months of age, the infant appeared alert and well. At this point in time, the measurements had fallen to below the 3–10th percentile for weight, and 10th percentile for length. The physical examination was otherwise unremarkable. In particular, there was no eczema or other skin abnormality. The paediatrician prescribed ranitidine (3 mg/kg per dose, three times daily) and suggested to introduce solids. However, symptoms continued unchanged, and the weight gain remained poor. The infant was referred for further specialist assessment at 6 months of age.

The paediatric gastroenterologist agreed with the diagnosis of GORD, which presented with frequent regurgitation and poor weight gain. There were no overt features of reflux oesophagitis, in particular no haematemesis. A barium meal demonstrated free reflux from the stomach into the oesophagus and did not show any evidence of gastric outlet obstruction or malrotation. Oesophageal 24-h pH monitoring was not performed as it was unlikely to provide additional relevant clinical information. A gastroscopy revealed no mucosal abnormalities in the oesophagus, stomach and duodenum. Endoscopic grasp biopsies showed a normal histological appearance in the upper oesophagus, but basal cell layer hyperplasia of 50%, six eosinophils per high power field and an increased number of epithelial neutrophils in lower oesophageal specimens. Findings in the gastric body and antrum were unremarkable. The duodenal villous architecture was preserved, and occasional eosinophils in the lamina propria were noted, raising the possibility of food protein allergy.

A diagnosis of food protein-induced GORD with mild-to-moderate reflux oesophagitis was made. In order to provide more effective acid suppression the infant was changed from ranitidine to omeprazole, 5 mg twice daily. In addition, in view of the duodenal findings, the formula was changed to an extensively hydrolysed formula. After an initial drop in oral intake caused by the taste difference, the infant accepted the new formula well, achieving a daily intake of approximately 100 ml/kg. The formula concentration was gradually increased to 420 kJ/100 ml to facilitate catch-up growth. Oral solids were continued and were kept free of cow's milk protein. Over the following 2 wk the regurgitation gradually diminished and the weight gain improved.

When reviewed at 8 months of age the regurgitation had resolved almost completely, and the proton pump inhibitor was discontinued. The weight gain over the previous 2 months had improved, with catch up to the 10–25th percentile, while the length had remained on the 10th percentile.

At 12 months of age a home challenge with cow's milk formula was conducted, starting with small volumes. Prior to the challenge, cow's milk-specific serum IgE levels (by CAP-FEIA) had been negative ($<0.35 \text{ kU}_A/\text{l}$), making IgE-mediated cow's milk allergy (CMA) unlikely. Weight and length had returned to the 25th percentiles, and the formula concentration was reduced to standard strength (280 kJ/100 ml). Challenge volumes of up to 30 ml of cow's milk formula per day were tolerated, but larger volumes (60 ml/day) were associated with a recurrence of large volume regurgitation. The home challenge was abandoned on day 6. The positive challenge confirmed a diagnosis of ongoing non-IgE-mediated cow's milk protein allergy and associated GORD. A repeat challenge with fresh cow's milk at 18 months was tolerated without a recurrence in symptoms, in keeping with the development of tolerance to cow's milk protein.

Discussion on GORD

Gastro-oesophageal reflux represents the passive flow of acidic gastric contents into the oesophagus (11). These reflux episodes occur predominantly during TLOSRS which is often triggered by distension of the gastric fundus (12). More than half of healthy infants regurgitate milk after feeds in the first months of life (13), and symptoms often resolve or improve significantly by 12 months of age (14). GOR is only considered pathological if it causes peptic mucosal injury, failure to thrive or respiratory complications (11). GOR is to be distinguished from vomiting which involves the active expulsion of gastric and duodenal contents (15). However, clinically it may be difficult to distinguish between GOR and vomiting in infants and young children (15, 16).

Several studies have linked GOR and oesophagitis in infancy to food allergy (17–20). In a study of infants with histological oesophagitis, about 42% improved after treatment with hydrolysed formula and relapsed on subsequent blinded challenges (18). The mechanisms by which food allergens induce GOR and oesophagitis are poorly understood. It has been suggested that release of proinflammatory mediators

from activated T cells and degranulated eosinophils may stimulate the ENS and cause peristaltic dysfunction or trigger TLOSRS (1, 4, 8, 9, 21–23). The absolute number of mucosal eosinophils in food protein-induced GORD is not increased ($\leq 5/\text{HPF}$) which distinguishes it from eosinophilic oesophagitis (eosinophils in upper and lower oesophageal biopsies $\geq 15\text{--}20/\text{HPF}$) (24, 25).

The case scenario illustrates a few typical features. Initially, the minor GOR symptoms without complicating features, such as haematemesis or failure to thrive, did not warrant any specific therapy. As regurgitation became more severe after the introduction of cow's milk-based formula, non-IgE-mediated CMA was considered in the differential diagnosis. In young infants with persistent vomiting, a gastric outlet obstruction (e.g. hypertrophic pyloric stenosis) should be excluded by ultrasound or barium meal. A barium meal is also useful to assess for intestinal malrotation. Although it has been suggested that oesophageal 24-h pH monitoring may be helpful in distinguishing non-allergic from food protein-induced GOR (26), other investigators have not confirmed this finding (20). Gastroscopy and grasp biopsies provide more useful diagnostic clues to guide the need for acid-suppressive therapy, or to rule out eosinophilic oesophagitis, as well as other food protein-induced upper gastrointestinal pathology (27, 28). Histological features of reflux oesophagitis include a low number of mucosal eosinophils ($\geq 5/\text{HPF}$) in lower oesophageal biopsies, in conjunction with basal layer hyperplasia, neutrophils and epithelial ulceration as evidence of acid-peptic injury (24). Eosinophilic oesophagitis is characterized by larger numbers of mucosal eosinophils ($> 15\text{--}20/\text{HPF}$) in the upper and lower oesophagus, without mucosal ulceration or neutrophilia (29). It is possible that reflux and eosinophilic oesophagitis co-exist at the same time. Importantly, the distinction between food protein induced and non-allergic GORD cannot be made by histology alone but relies on a diagnostic trial of food protein elimination and challenge (1).

Although skin prick testing or measurement of cow's milk-specific serum IgE are not helpful in making a diagnosis of gastrointestinal food allergy, these tests may be useful before a food challenge. If negative, the challenge can generally be performed outside the hospital setting. Use of the atopy patch test has been suggested for the diagnosis of food protein-induced GOR, but the evidence so far is only based on small case series (30).

Most infants with food protein-induced GORD will respond within 2 wk to treatment with either extensively hydrolysed or amino acid-based formula. In malnourished infants, the energy density of the formula needs to be gradually increased to provide adequate energy for catch up growth. The introduction of solids should be attempted between 4 and 6 months of age. Some infants may have a relapse of symptoms after the introduction of specific food proteins, such as wheat or soy. Acid suppression with a proton pump inhibitor is effective in treating reflux oesophagitis, although it will not necessarily reduce the frequency of regurgitation. Rarely, infants with a delayed diagnosis of food allergy and ongoing regurgitation may develop complete feeding refusal, requiring nasogastric tube feeding. Fundoplication (in neurologically intact infants) can often be averted if underlying food allergy is recognized and treated. Fortunately, most infants will improve towards 12–18 months of age, which also coincides with age of remission of CMA (2).

Case 2

A 3-wk-old boy presents with persistent abdominal distension and infrequent defaecation. He was born via normal vaginal delivery at term after an uneventful pregnancy. His birth weight was 3.4 kg, and his length 49 cm. Meconium was passed within 24 h of delivery. His mother initially attempted breast feeding but discontinued after 1 wk as because of mastitis requiring antibiotic treatment. Because of a positive family history of atopy, the infant was commenced on a partially hydrolysed formula. From the first week of life the infant passed stools every 4–5 days. Stools were of toothpaste consistency, with some mucus, but there was no visible blood. His parents describe that the infant's feeding would deteriorate until a stool has been passed once or twice per week. Before defaecation the infant often became distressed and seemed to strain excessively. On examination, he had a soft and moderately distended abdomen. There was no palpable organomegaly or mass. His perineal anatomy was unremarkable with a normally formed anal sphincter. A rectal examination revealed some soft faeces in the rectum, and there was no apparent anal stenosis. The physical examination was otherwise normal. The infant was commenced on oral lactulose, 3 ml with each bottle of formula. However, when reviewed

10 days later there had been no significant change in stool frequency. A referral was made to a paediatric surgeon to exclude Hirschsprung's disease, and a rectal suction biopsy performed at 7 wk of age. The biopsy demonstrated presence of normal ganglia in the submucosa, making Hirschsprung's disease unlikely. As an incidental finding, the pathologist noted increased numbers of mucosal eosinophils. This finding led to a provisional diagnosis of food protein-induced proctocolitis with faecal retention. The infant was changed to an amino acid-based formula (AAF). Within days of the formula change there was a noticeable increase in stool frequency, with normal bowel motions every 2–3 days. The subsequent clinical course was relatively uneventful. The abdominal distension and tenesmus gradually decreased. His parents noticed a recurrence of symptoms when solids were introduced around 6 months of age. However, the symptoms resolved spontaneously within 1–2 wk. The infant remained on AAF until 12 months of age when foods containing cow's milk protein were cautiously introduced without problems.

Discussion on infantile constipation

Chronic constipation is characterized by the infrequent passage of hard stools for more than 8 wk, in association with either faecal incontinence, withholding behaviour or painful defaecation (31). The vast majority (97%) of constipation in young children is believed to be functional (32), and is frequently associated with painful defaecation, stool withholding and overflow incontinence (33). In American children, the prevalence of constipation was 2.9% in the first year (32). Constipation with onset in early infancy is more likely to be associated with primary motility disorders (e.g. Hirschsprung's disease, slow transit constipation) or anatomical abnormalities (e.g. anal stenosis, anterior anal sphincter) (34). Treatment relies on use of laxatives or stool softeners, dietary change and toilet training in older children (32, 33, 35). Although CMA has been shown to be a cause of constipation in a subset of children, the exact proportion is unclear (36–38) and the pathophysiological mechanisms have remained elusive (32, 39, 40). Allergic proctocolitis is typically associated with rectal bleeding, passage of mucus and low-grade diarrhoea (4, 41). However, a recent study presented a case series of infants with constipation and eosinophilic proctocolitis (38).

Food protein-induced constipation is a poorly defined clinical entity, and its incidence in infancy is therefore not known. Only a small fraction of constipation in children under 2 years is thought to be caused by allergy, and the vast majority is functional in nature (32). Minor non-allergic constipation commonly occurs at the transition from breast to formula feeding. Cow's milk formulae with a high casein:whey protein ratio and high levels of palmitic acid have been shown to negatively affect stool consistency (42). More recently, the absence of bifidogenic prebiotic oligosaccharides in infant formula has been suggested as a cause for infantile constipation (43). The term 'food protein-induced constipation' implies that the disorder is mediated by immunological effects of cow's milk protein. Presence of increased numbers of eosinophils on rectal mucosa may provide indirect evidence for food allergy in these infants (38). A change to a different cow's milk formula in these infants typically does not lead to clinical improvement, and treatment with extensively hydrolysed or amino acid-based formula within 4 wk is recommended.

As for GOR, there is no single diagnostic marker for a diagnosis of cow's milk protein-induced constipation. The infant in the second case study suffered from faecal retention rather than true constipation with hard stools. The early onset of symptoms in relation to the introduction of formula and the finding of eosinophilic proctocolitis made non-IgE-mediated food allergy likely. The diagnosis was further supported by a clear response to dietary elimination of cow's milk protein. Importantly, anatomical causes for obstructed defaecation or Hirschsprung's disease had been excluded.

Iacono et al. (37) described a group of older children with constipation and rectal eosinophilia who improved after treatment with soy-based diet and cow's milk elimination for 2 wk. However, as older children with long-standing constipation may have developed secondary megarectum with blunting of rectal sensation, the response to dietary change in this age group may be delayed and less clear. Stool softeners or laxatives should therefore be continued during a dietary trial and gradually weaned, as tolerated. A re-biopsy may be required to demonstrate resolution of the eosinophilic proctocolitis. The prognosis of food allergic constipation appears to be generally good. The dietary restrictions need to be maintained until tolerance to the offending foods has been demonstrated.

Case 3

A 3-wk-old boy presents with persistent, unexplained crying and feeding refusal. He was born at term after an uneventful pregnancy. His birth weight was 2.9 kg. He is exclusively breast-fed. His mother describes that from the age of 3 days the infant has been very unsettled, crying inconsolably for several hours in the early evening. During breast-feeding, the infant becomes distressed, back-arches and pushes away from the breast. As a result, his oral intake has been poor with somewhat slow weight gain. Apart from these feeding difficulties, he is well. There is only minor regurgitation after feeds, which does not appear to be associated with immediate distress. His physical examination and developmental assessment are within normal limits. A urine specimen collected at 4 wk of age was unremarkable. A provisional diagnosis of infantile colic was made. Parents were at that stage reassured and provided with written advice about settling techniques. When reviewed 1 wk later, the situation was unchanged and his mother appeared increasingly exhausted. Given the protracted course, his mother commenced a multiple food elimination diet, as supervised by a dietitian. She eliminated cow's milk, wheat, egg and peanut/nuts from her diet, while maintaining an intake of vegetables, other grains, fruit, meats, fish and soy milk. A calcium supplement of 1.2 g/day, as well as a multi-vitamin preparation, was recommended. Over the following 2 wk there was significant improvement in the infant's behaviour. An attempt to reintroduce wheat into the mother's diet at 8 wk of age failed caused by a significant increase in irritable behaviour. However, 2 months later the reintroduction of wheat was tolerated. Reintroduction of cow's milk protein-containing foods was attempted at regular intervals but was associated with increased unsettled behaviour until 7 months of age. Thereafter, his mother could gradually normalize her diet without an increase in infant irritability. Introduction of complementary solids was attempted from about 5 months without problems. No further adverse reactions to foods were observed, and the infant was discharged from follow-up at 12 months of age while tolerating an unrestricted diet.

Discussion on infantile colic

Unexplained episodes of irritability, fussing, or crying for more than 3 h/day, on more than

3 days/wk and for at least 3 wk are often referred to as 'infantile colic' (44). This condition affects up to 19% of infants in the first months of life (45, 46). Less than 5% of distressed infants have an identifiable medical explanation for their crying (44), while developmental and interactive factors play a significant role (44, 47, 48). Although the term 'colic' implies a gastrointestinal pathology, the aetiology is most likely multifactorial. As a result of the response to hypoallergenic formula or maternal dietary modification, infantile colic is commonly considered a clinical presentation of non-IgE-mediated gastrointestinal food allergy (2, 4, 49, 50). However, there is only indirect evidence for gastrointestinal abnormalities and motility disturbances, including abnormal intestinal permeability (51), elevated serum motilin levels in infants with colic (52) or clinical improvement after treatment with anticholinergic drugs (e.g. dicyclomine or cimetropium bromide) (53, 54). The natural history of infantile colic is believed to be favourable, and most infants improve significantly around 3–4 months of age. A subgroup of infant progress to the 'persistent infant–mother distress syndrome' (44), often in association with ongoing food allergies (45, 55). However, a large prospective study of 983 infants found no evidence of an increased risk for asthma and other atopic disorders in infants with colic (56).

Apart from dietary interventions, it is important to provide general support and respite for the family. Mother–infant units that teach feeding and settling techniques have specialized in the treatment of infants with severe colic. Several clinical trials have demonstrated that hypoallergenic formulae or maternal elimination diets improve symptoms in infants with colic (53, 53, 57–60). A systematic review of these studies found a significant protective effect for extensively hydrolysed formulae, but not for soy, partially hydrolysed or lactose-reduced cow's milk-based formulae (53). Recent case reports have suggested that amino acid-based formula may also be effective in reducing persistent crying (61, 62). However, breast-feeding *per se* is not protective against infantile colic (55). Transfer of intact food antigens into breast milk may expose the infant's intestinal mucosa to potential allergens that are able to elicit immunological responses (57, 63).

A recent randomized study in breast-fed infants under 6 wk of age with colic demonstrated a significant benefit of a low-allergen

maternal elimination diet of at least 1-wk duration (57). However, it can be difficult to eliminate the right range of foods without being overly restrictive. Many practitioners will commence with the elimination of cow's milk, before recommending more complex elimination diets. It is important to have a defined end-point and to monitor the nutritional adequacy of the diet for mother and infant. Supervision of elimination diets should ideally involve a dietitian. The response to diet should be assessed within 2 wk. Once the infant has improved, either spontaneously or in response to dietary change, step-wise reintroduction of the eliminated foods should be attempted as soon as possible.

Table 1. Clinical features suggestive of food protein-induced gastrointestinal motility disorders in infants and young children

Overarching features
Early onset of symptoms within the first weeks of life
Failure to respond to standard medical therapy
Significant clinical improvement after cow's milk protein elimination from infant's (hypoallergenic formula) or mother's diet (maternal elimination diet)
Relapse of symptoms after re-introduction of offending food protein
Co-existence of infantile colic, gastro-oesophageal reflux symptoms and constipation points to possible underlying non-IgE-mediated gastrointestinal food allergies
Gastro-oesophageal reflux disease
Frequent regurgitation, often large in volume
Commonly associated with aversive feeding behaviours and distress during feeding
Histological evidence of reflux oesophagitis with minor tissue eosinophilia
(<5 eosinophils/HPF), basal layer hyperplasia, tissue neutrophilia and epithelial erosions
Significant improvement of symptoms within 2–4 wk on hypoallergenic formula (often incomplete response)
Differential diagnosis: eosinophilic oesophagitis
Constipation
Moderate-to-severe constipation
Worsening of symptoms after first dietary introduction of cow's milk protein
Excessive straining despite apparently soft stool consistency
Irritability before defaecation (tenesmus?)
Need for high-dose laxatives or bowel wash-outs in first 12 months of life
Rectal biopsy reveals mucosal eosinophilia (eosinophilic proctocolitis)
Manometry: high internal anal sphincter resting tone
Differential diagnosis: Hirschsprung's disease, anorectal malformations, slow transit constipation
Infantile colic
Onset within first week of life in breast-fed infants
Persistent crying for more than 3 hours per day beyond 3 months of age
Commonly associated with GOR symptoms and frequent regurgitation
Aversive feeding behaviours and distress during feeding
Slow weight gain and failure to thrive
Irritability may fluctuate according to mother's diet (e.g. cow's milk intake)
Differential diagnosis: neuro-developmental disorders

Conclusion

Gastro-oesophageal reflux disease, constipation and colic are common clinical problems in infants and young children. In a subset of infants presenting with these functional disorders, non-IgE-mediated food protein allergy contributes significantly to the disease process. The diagnosis of food protein-induced gastrointestinal motility disorders is hampered by the absence of specific clinical features or useful laboratory markers, and treatment is often empirical. Clinical features that suggest a food protein-induced aetiology in these conditions include onset in early infancy, close relationship to the first dietary introduction of cow's milk protein or a failed trial of standard medical therapy (Table 1). Gastrointestinal biopsies before commencing a hypoallergenic diet may provide the most important diagnostic clues. Early recognition and referral are therefore essential for the optimal management of these patients to prevent nutritional sequelae or aversive feeding behaviours. Further research is urgently required to better define the pathological mechanisms and diagnostic markers of paediatric allergic gastrointestinal motility disorders.

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