Cow's-Milk Allergy Is a Risk Factor for the Development of FGIDs in Children

Miguel Saps, Peter Lu, and Silvana Bonilla

ABSTRACT

Objectives: Functional gastrointestinal disorders (FGIDs) are common in children. Their pathogenesis remains unknown and is most likely multifactorial. We hypothesized that noninfectious causes of inflammation affecting the gastrointestinal (GI) tract early in life, such as cow's-milk allergy (CMA), can predispose to the development of FGIDs later in childhood.

Patients and Methods: Case-control study. Subjects were patients between 4 and 18 years diagnosed with CMA in the first year of life at Children's Memorial Hospital in Chicago, IL, between January 2000 and June 2009. Diagnosis of CMA was based on history and clinical findings. Siblings 4 to 18 years of age without a history of CMA were selected as controls. Cases completed the parental form of the Pediatric Gastrointestinal Symptoms Rome III version questionnaire to assess for GI symptoms.

Results: Fifty-two subjects (mean age 8.1 ± 4.48 years, 62% girls) and 53 controls (mean age 9.7 ± 4.20 years, 55% girls) participated in the study. Twenty-three of 52 subjects (44.2%) reported GI symptoms that included abdominal pain, constipation, or diarrhea compared with 11 of 53 controls (20.75%) (odds ratio 3.03, $P = 0.01$). Abdominal pain was significantly more common in cases (16/52, 30.8%) versus controls (5/53, 9.43%) (odds ratio 4.27 [1.43–12.7]) ($\chi^2 = 7.47$, $P = 0.01$). Abnormal stool habits were more common in cases (15/52, 28.8%) versus controls (7/53, 13.2%), but the difference was not statistically significant. Ten of 52 subjects (19.2%) met the Questionnaire on Pediatric Gastrointestinal Symptoms Rome III version criteria for diagnosis of an FGID (7 irritable bowel syndrome, 2 functional dyspepsia, 1 functional abdominal pain), whereas none in the control group did.

Conclusions: CMA constitutes a risk factor for the development of FGIDs in children.

Key Words: abdominal pain, cow's-milk allergy, functional gastrointestinal disorders, gastrointestinal symptoms, infancy

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Functional gastrointestinal disorders (FGIDs) are common in children. The pathogenesis of FGIDs remains elusive and is probably multifactorial. Among the multiple factors thought to play a role in the pathogenesis of FGIDs are early-life events. Adult and pediatric studies have found visceral hypersensitivity in a large proportion of patients with FGIDs (1,2). FGIDs may occur following acute gastroenteritis including irritable bowel syndrome (IBS) in up to 36% of cases (3). Postinfectious IBS is thought to be the result of low-grade inflammation and visceral hypersensitivity that persists after the acute infection has resolved (4). Animal studies have shown that in neonatal rats, chemical irritation of the colon results in visceral hypersensitivity days after the acute inflammation has resolved (5). This phenomenon does not occur if a similar experiment is conducted in adult rats (6). Together, these studies point toward a predominantly neurogenic mechanism that is more pronounced when the inflammation occurs early in life. It has been hypothesized that colonic hypersensitivity could be caused by functional changes in the nervous system (7). The animal model of early-life events cannot be replicated in humans. Understanding whether the presence of colonic inflammation in the first weeks of life increases the risk of developing FGIDs could greatly advance our present knowledge of the pathogenesis of FGIDs.

Cow's-milk protein allergy (CMA) affects about 2% to 5% of infants (8). CMA usually occurs in the first months of life following the introduction of cow's-milk–based formula and is associated with gastrointestinal (GI) inflammation. CMA is generally of a self-limiting nature and resolves in the first 2 years of life as children become progressively tolerant to cow's-milk protein (9). CMA may constitute a human model that mimics early-life inflammation in animal studies. We hypothesize that noninfectious causes of inflammation affecting the GI tract early in life, such as CMA, can predispose to the development of FGIDs later in childhood.

PATIENTS AND METHODS

Study Population

The study comprised a cohort of patients diagnosed with CMA in the first year of life at Children's Memorial Hospital in Chicago, IL, between January 2000 and June 2005. Charts with the *International Classification of Diseases-9* codes 558.3 (allergic gastroenteritis and colitis) (10) with a present age of 4 to 10 years were reviewed by a single pediatric gastroenterologist (M.S.) to confirm the diagnosis of CMA and exclude those with concomitant comorbidities. Diagnosis was based on clinical symptoms following present American Gastroenterological Association guidelines on the evaluation of food allergy in gastrointestinal disorders (11). Biopsies were available in only 2 cases. Parents of children with CMA (cases) were contacted via telephone and enrolled in the study at that time. Parents were asked to review the child's history and complete the parental Questionnaire on Pediatric Gastrointestinal Symptoms Rome III version (QPGS-RIII) (12). QPGS is a validated questionnaire for the diagnosis of FGIDs in children older than 4 years. Due to their similar genetic, environmental, and socioeconomic backgrounds that can play a role in the prevalence of FGIDs, siblings 4 to 18 years of age without a history of CMA were selected as controls. Each index case was assigned a unique control.

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From the Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Gastrointestinal Motility and Functional Bowel Disorders Program, Children's Memorial Hospital, Northwestern University, Chicago, IL.

Address correspondence and reprint requests to Dr Miguel Saps, MD, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Memorial Hospital, 2300 N Children's Plaza, PO Box 57, Chicago, IL 60614 (e-mail: msaps@childrensmemorial.org).

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If patients did not have siblings or the siblings had a history of CMA, then siblings of other children with CMA were used as controls. All of the parents provided informed consent on the telephone before participation. The study was approved by the internal review board of Children's Memorial Hospital.

Sample Size

Sample size calculation was based on the assumption that 30% of the subjects with CMA would develop FGIDs compared with 5% in the control group. Given these estimates, with a nondirectional α of 0.05 and a power of 0.90, 49 patients per group were required to detect this level of difference (13).

Statistical Analysis

Unadjusted odds ratios (OR) for CMA as a risk factor for FGIDs were calculated. χ^2 analysis was performed to evaluate differences in GI symptoms between the 2 groups. Logistic regression modeling with proportional odds assumption was applied to identify interactions between age, sex, and CMA. Statistical significance was defined as a P value of <0.05. The analysis was conducted using SAS 9.1 software (SAS Institute, Cary, NC).

RESULTS

Study Population

Fifty-two subjects (mean age 8.1 ± 4.48 years, 62% girls) and 53 controls (mean age 9.7 ± 4.20 years, 55% girls) agreed to participate and completed the QPGS-RIII (Table 1). The presence of GI symptoms at the time of diagnosis was confirmed in all of the children with CMA. These symptoms included constipation, diarrhea, hematochezia, failure to thrive, and vomiting. Ten (16%) of all children diagnosed as having CMA were excluded following a thorough chart review due to the presence of concomitant organic disease processes (diabetes mellitus and cystic fibrosis) or lactose intolerance as documented by breath hydrogen test or disaccharidase testing. We were able to successfully match 38 patients with CMA with healthy siblings. Two patients with CMA had a sibling with CMA. A control from the pool of siblings of children with CMA who were younger than 4 years at the time of the study was selected for these 2 children and for the 13 remaining patients who had no siblings or had a sibling of younger than 4 years or older than 18 years. Two patients provided no information regarding formula changes. One patient was switched to soy formula. The remaining patients received either hydrolyzed or elemental formula or abstained from dairy products.

Gastrointestinal Symptoms

Twenty-three of 52 subjects (44.2%) reported GI symptoms that included abdominal pain, constipation, or diarrhea compared with 11 of 53 controls (20.75%) (unadjusted OR 3.03 [1.28–7.16]) ($\chi^2 = 6.61$, $P = 0.01$). Abdominal pain was significantly more common in cases (16/52, 30.8%) versus controls (5/53, 9.43%) (unadjusted OR 4.27 [1.43–12.7]) ($\chi^2 = 7.47$, $P = 0.01$). Abnormal stool habits were more common in cases (15/52, 28.8%) versus controls (7/53, 13.2%), but the difference was not statistically significant. However, reporting both abdominal pain and abnormal stool habits was much more common in cases (8/52, 15.4%) versus controls (1/53, 1.89%) (unadjusted OR 9.46 [1.14–78.6]) (Yates $\chi^2 = 6.10$, $P = 0.01$). Ten of 52 subjects (19.2%) met the QPGS-RIII criteria for diagnosis of an FGID (7 irritable bowel syndrome, 2 functional dyspepsia, 1 functional abdominal pain), whereas none in the control group did. This difference was statistically significant after controlling for age and sex ($P = 0.001$).

TABLE 1. Characteristics of the sample

	Cases (N = 52)	Controls (N = 53)
Female, %	62	55
Age, mean ± SD, y	8.1 ± 4.48	9.7 ± 4.20
Gastrointestinal symptoms, % (n/N)	44.2 (23/52)	20.7 (11/53)
Abdominal pain	30.8 (16/52)	9.43 (5/53)
Abnormal stool habits	28.8 (15/52)	13.2 (7/53)
Rome II diagnosis, % (n/N)	13.4 (7/52)	—

DISCUSSION

Our study links for the first time CMA and FGIDs, 2 common conditions in children. The pathogenesis of FGIDs remains unknown. FGIDs are thought to result from the interaction of multiple factors affecting the child at different times during development. Among these factors, inflammation and early-life events seem to play an important role. GI inflammation secondary to infectious agents and Henoch-Schönlein purpura has been linked to the onset of FGIDs in children (14). Nerve remodeling of vagal afferent fibers and alterations in mechanosensitive properties have been found in rats following gastric surgery (15). Gastric suction at birth has been associated with the development of FGIDs later in life in humans and animals (16). Animal studies have also stressed the importance of early-life insults in the development of hypersensitivity (17). Psychological or biological stressful events occurring soon after birth result in increased GI permeability during both the neonatal and adult period and favor the occurrence of IBS later in life (18). Studies have shown that colonic inflammation during an early vulnerable period of neural plasticity leads to long-lasting hypersensitivity that outlasts the acute inflammation (6). Our study proposes for the first time a model that mimics the animal model of early colonic inflammation. We surveyed a large group of children diagnosed with CMA early in life several years after their initial diagnosis. We found a higher frequency of GI symptoms and FGIDs in children diagnosed with CMA than in healthy controls. Our study showed that 44.2% of children with a history of CMA reported GI symptoms including abdominal pain, constipation, or diarrhea compared with 20.75% of controls in long-term follow-up. Nineteen percent of the patients and none of the controls were diagnosed with an FGID using strict diagnostic criteria. Studies have shown an association between history of CMA and constipation in children 2 to 3 years old. Although we found a higher percentage of children with constipation among those with a previous history of CMA, the difference was not significant. However, we found a significantly higher likelihood of an association of constipation with alteration of stooling pattern (OR 9.46), which is consistent with the diagnosis of IBS.

Histological findings associated with CMA include the presence of cellular infiltrates and marked increase in eosinophils in the mucosa and submucosa with involvement of even deeper muscular layers in some cases (19,20). Although the immunopathogenic mechanism of CMA is not fully understood, eosinophils and their degranulation products seem to play an important role. Eosinophil activation and degranulation may result in acute and long-lasting effects. Studies have linked the presence of T helper 2–associated eosinophilic inflammatory response to GI allergic hypersensitivity and gastric dysmotility (21). A potential mechanistic role for eotaxin and eosinophils in GI allergic hypersensitivity has been

suggested in prior studies, which showed eosinophils in the vicinity of damaged axons on mice exposed to food antigens (22). Close proximity of eosinophils and epithelial cells was found in tissues affected by allergic gastroenteropathy (23). Eosinophil granule major basic protein (MBP) decreases epithelial colonic barrier function (7). Increased intestinal permeability has been associated with both CMA and the pathogenesis of FGIDs (24). A study (25) has shown higher colonic permeability and GI inflammation in children with functional abdominal pain and IBS than in healthy controls. It is likely that in patients with CMA the detrimental effect of cellular infiltration and their products on visceral nerve fibers is facilitated by the increased permeability found in this condition that allows them to reach deeper levels. Sensitization of the corresponding spinal segments may result in further amplification of afferent input. The combined effect of these factors may explain the presence of short- and long-term alterations in sensation and motor function that was found in our study. Dysmotility and visceral hypersensitivity are some of the proposed mechanisms of FGIDs. These factors may also play a role in CMA. CMA has been associated with dysmotility, constipation, and excessive crying in infants (17,26,27). Hypersensitivity may lead to altered perception of physiological stimuli such as intestinal distention and peristalsis being perceived as painful events (allodynia). CMA-associated dismotility and constipation may increase pain even further. These mechanisms should be considered in the context of a vulnerable age such as infancy. Early-life events are increasingly recognized as important modulating factors in patients with FGIDs. The first few months of life constitute a vulnerable period in the developing nervous system. Early-life inflammation can cause long-term changes in the brain–gut axis that may ultimately result in central sensitization, altered pain pathways, and persistent visceral hyperalgesia. In our study, not all of the children diagnosed with CMA developed FGIDs. Possible explanations include the fact that the inflammatory response and severity of CMA may vary from child to child. Some of the children in our study may have completely resolved the acute inflammation, whereas others may have persistent subtle inflammation such as the case of postinfectious IBS. In keeping with the biopsychosocial model, we believe that a spectrum of severity of pain perception and behavioral response to pain exists and that it results from the interaction of multiple biological, psychological, and social factors. Genetic, environmental factors, and parental reaction to the child's pain may modulate the child's pain perception and behavioral response to pain. To control for some of these factors we selected children of similar genetic, environmental, and social background as controls.

The fact that most patients in the study received a hypoallergenic diet, with a large percentage developing symptoms at follow-up, raises some considerations. It is possible that the institution of treatment at the time of the clinical presentation of CMA may be futile for the purposes of preventing long-term GI symptoms. On the basis of the data of studies showing that a relatively innocuous maneuver such as gastric suction at birth is enough to predispose children to FGIDs later in life, it is probable that infants with several weeks or months of ongoing inflammation may have been sensitized by the time the treatment was initiated. Alternatively, hypoallergenic formulas, although effective to abort acute symptoms, may not be effective to prevent FGIDs.

There are some limitations to our study. The design of our study does not allow us to exclude the possibility of recall bias. Parents who reported persistence of symptoms may not accurately recall whether the GI symptoms of their child improved transiently and recurred at a later time. Parents may also recall more vividly details on the GI symptoms from a child who had a GI condition at birth than those from a healthy sibling. The lack of pathological confirmation of the CMA diagnosis constitutes another limitation of our study. Patients were categorized as having CMA on the basis of the physician's clinical suspicion following recent diagnostic recommendations by the American Gastroenterological Association (11). Conducting routine endoscopy in a transient and benign condition is not justified in clinical practice. Empirical exclusion of cow's-milk protein from the infant diet is widely accepted as standard management (11). We cannot exclude that some of the patients labeled as having CMA may have a different unspecified condition or that parents were more eager to report symptoms that may have been interpreted as CMA by the practitioner. Future prospective studies should be designed to overcome the shortcomings of our investigation.

In conclusion, CMA seems to constitute a risk factor for the development of FGIDs in children. If future prospective studies corroborate our findings, then the risk of developing FGIDs should be considered in the prognosis of CMA in children.

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