Postinfectious Functional Gastrointestinal Disorders in Children: A Multicenter Prospective Study

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Objectives To prospectively investigate the occurrence of postinfectious functional gastrointestinal disorders (FGIDs), diagnosed according to the Rome III criteria, in children with acute diarrhea of different infectious etiology.

Study design This was a prospective cohort multicenter study. Children 4-17 years of age presenting with acute diarrhea who tested positive for an enteric infection were recruited within 1 month from the episode and matched with control subjects of similar age and sex. Symptoms were evaluated with a validated questionnaire for FGIDs at the time of enrollment in the study and after 3 and 6 months.

Results A total of 64 patients (36 boys; median age 5.3 years; age range 4.1-14.1 years) were recruited, 32 subjects in each arm. Infections included rotavirus (56.8%), salmonella (30%), adenovirus (6.6%), norovirus (3.3%), and *Giardia lamblia* (3.3%). FGIDs were significantly more common in exposed patients compared with controls within 1 month from acute diarrhea (40.6% vs 12.5% [$P = .02$, relative risk (RR) = 1.9]), 3 months (53% vs 15.6% [$P = .003$, RR = 2.2]), and 6 months (46.8% vs 15.6% [$P = .01$, RR = 1.9]) later. No correlation was found between different etiologies, age, or sex, and any type of FGIDs. Among exposed children, abdominal pain–related FGIDs were significantly more frequent compared with controls after 6 months from infection ($P = .04$, RR = 1.7).

Conclusion This prospective cohort multicenter study supports postinfectious FGIDs as a true entity in children. There seems to be a significant increase in abdominal pain–related FGIDs after acute diarrhea in children within 1 month and 3 and 6 months later. *(J Pediatr 2015;166:903-7)*.

Functional gastrointestinal disorders (FGIDs) are defined as a variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. There is evidence in the literature supporting the existence of postinfectious FGIDs (PI-FGIDs) as a true entity in adults.[1-5] In adults, irritable bowel syndrome (IBS), one of the most common FGIDs, can occur after a gastrointestinal infection resulting in transient inflammation. Gweel[1] showed that 20%-25% of adult patients admitted to the hospital for bacterial gastroenteritis developed symptoms consistent with IBS within the next 3 months. Parry et al[2] reported that symptoms consistent with IBS and functional diarrhea occur more frequently in adults after a bacterial gastroenteritis compared with controls (29% vs 2.9%), even after careful exclusion of subjects with preexisting FGIDs. Inflammatory stimuli may trigger a visceral hyperalgesic state and alter the bowel motor function in patients with IBS. A systematic literature review[3] reported that the incidence of postinfectious IBS (PI-IBS) ranges between 7% and 36% after epidemic infections, between 4% and 36% after individual infections, and between 4% and 14% after traveler's diarrhea. Nearly 10% of patients with an intestinal bacterial infection report postinfectious symptoms up to 10 years after the initial event.[4] They represent a clinically challenging population with high psychiatric comorbidity and somatic symptom burden.[4]

A meta-analysis[5] showed that risk factors for the development of PI-IBS include female sex, younger age, severity of the initial gastrointestinal insult, duration of the enteritis, and adverse psychological factors. In children, we previously confirmed the existence of PI-FGIDs in a multicenter cohort study.[6] In that population there was a statistically significant increase in cases of FGIDs

AP-FGID	Abdominal pain-related functional gastrointestinal disorder
FGID	Functional gastrointestinal disorder
IBS	Irritable bowel syndrome
PI-FGID	Postinfectious functional gastrointestinal disorder
PI-IBS	Postinfectious irritable bowel syndrome
QPGS-RIII	Rome III Diagnostic Questionnaire for the Pediatric Functional Gastrointestinal Disorders

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(mostly IBS) after acute bacterial gastrointestinal infections: 36% of exposed patients and 11% of controls reported chronic abdominal pain when contacted at least 6 months after the visit. Another study[7] suggested that rotavirus infection does not place children at increased risk for abdominal pain-related FGIDs (AP-FGIDs) at long-term follow-up. The aim of the present study was to investigate the occurrence of PI-FGIDs, according to the Rome III criteria,[8-10] in children with acute diarrhea of any infectious etiology.

Methods

This prospective cohort study was conducted in 6 pediatric departments in Italy (Catanzaro, Foggia, L'Aquila, Bari, Varese, Napoli) from 2007 to 2010. The study was approved by the independent ethics committees of the participant centers. Informed consent was obtained by parents or guardians of each recruited subject.

The inclusion criteria were as follows: age between 4 and 17 years, acute diarrhea with positive stool culture or parasite or viral tests performed in the same participants' hospitals, recruitment within 1 month from the infection, completion of the Questionnaire for the Pediatric FGIDs, Italian-speaking subjects, and informed consent obtained. The exclusion criteria were as follows: age younger than 4 years or older than 17 years; lack of positive stool tests; recruitment beyond 1 month from acute diarrhea; presence of neurologic impairment; recent surgery; celiac disease; inflammatory bowel disease; cystic fibrosis; food allergies; transplantation; immunosuppression; liver, renal, metabolic or rheumatologic diseases; and inability to communicate. We also excluded patients who did not have a 6-month follow-up.

The "exposed group" was identified as subjects, consecutively enrolled, with proven infectious acute diarrhea, on the basis of a single positive stool test; during follow-up, stool tests were not repeated. Acute diarrhea was defined as the presence of at least 3 liquid stools in 24 hours lasting >3 days but <2 weeks. Acute diarrhea was defined as severe when the affected child was diagnosed clinically with dehydration during the acute illness. For each patient that was successfully enrolled, another child of similar age and sex presenting to the same hospital in the emergency department or at an outpatient clinic for evaluation of minor trauma or for a well-child visit within 4 weeks of the index case was recruited as a control.

The presence of FGIDs was assessed through a standardized questionnaire, the Rome III Diagnostic Questionnaire for the Pediatric Functional Gastrointestinal Disorders (QPGS-RIII).[10] The QPGS-RIII is an age-appropriate, structured questionnaire and constitutes a shorter form of the Questionnaire on Pediatric Gastrointestinal symptoms[11,12] that has undergone preliminary validation.[13,14] The parent-report version of the QPGS-RIII was completed by parents of children between 4 and 10 years of age; the self-report version of the QPGS-RIII was completed by children 10 years of age and older. The QPGS-RIII includes sections assessing children's bowel habits, abdominal pain, and other gastrointestinal symptoms, as well as limitations in activities, and was completed 3 times: (1) at the time of enrolment in the study (within 1 month from the positive stool tests); (2) after 3 months; and (3) after 6 months from the enrolment in the study. The questionnaire was filled in during an outpatient visit or by a standardized telephone interview performed by the same doctor in each center.

Statistical Analyses

Descriptive data for categorical variables are presented as percentages or ratios. We constructed tables of frequency for comparison with a control arm for the number of children who reported FGIDs at the time of the enrolment on the study and 3 and 6 months later. Analyses for comparisons between groups were performed using the χ^2 test for categorical variables or by Fisher exact test as appropriate. Statistical significance was assumed at $P \leq .05$.

Results

Sixty-four patients (36 boys; median age 5.3 years; age range 4.1-14.1 years) were recruited, 32 children in each arm. The median age of the exposed patients (18 males, 14 females) was 5.55 years (age range = 4.1-14.1), the median age of the unexposed patients (18 males, 14 females) was 5.2 years (age range = 4.5-12.1). There were no significant demographic differences between the exposed and control groups at enrollment. Subjects in the exposed group had positive stool testing for rotavirus (n = 17, 56.8%), salmonella (n = 11, 30%), adenovirus (n = 2, 6.6%), norovirus (n = 1, 3.3%), and *Giardia lamblia* (n = 1, 3.3%). Diagnosis of FGIDs was significantly more frequent in exposed patients compared with controls within 1 month from acute diarrhea (40.6% vs 12.5% [$P = .02$, relative risk (RR) = 1.9]), 3 months later (53% vs 15.6% [$P = .003$, RR = 2.2]), and 6 months later (46.8% vs 15.6% [$P = .01$, RR = 1.9]). Demographic characteristics of exposed patients in whom a PI-FGID developed are shown in **Table I**. The prevalence of subtypes of FGIDs diagnosed according to Rome III criteria among exposed

Table I. Demographics of all exposed patients and of exposed patients in whom PI-FGIDs were diagnosed within 1 month and 3 and 6 months after an acute diarrhea

	Exposed	PI-FGIDs within 1 month	PI-FGIDs 3 months later	PI-FGIDs 6 months later
Median age, y (range)	5.55 (4.1-14.1)	4.9 (4.6-10.3)	5.2 (4.4-11.3)	4.9 (4.7-14.1)
No. boys	18	6	10	7
No. girls	14	7	7	8

and unexposed patients within one month from enrollment, 3 and 6 months later are shown in **Tables II** and **III**, respectively.

We did not find any significant correlation between severity of acute diarrhea (15/32 exposed patients developed dehydration during the acute diarrhea) and either an increased frequency of FGIDs or with any subtypes of AP-FGIDs diagnosed at the 3 follow-up visits (5/15 had FGIDs within 1 month vs 8/17 who did not have severe acute diarrhea; 7/15 at 3 months vs 10/17; 9/15 at 6 months vs 6/17, P = not significant for all).

Etiologies of acute diarrhea in the children reporting FGIDs within 1 month and 3 and 6 months later are shown in **Figure 1** (available at www.jpeds.com). No correlation was found between different etiologies, age, or sex, and any specific type of FGIDs. At 6 months, FGIDs were diagnosed in 9 of 20 (45%) children with viral infections and in 6 of 11 (54.5%) of those with bacterial infections (P = not significant). Among exposed children, AP-FGIDs were diagnosed with increased frequency in the exposed group at subsequent follow-up visits (18.7% at 1 month, 25% at 3 months, and 28.1% at 6 months), with significant difference compared with controls achieved at 6 months (P = .04, RR = 1.7) (**Figure 2**). Among AP-FGIDs, the prevalent subtypes were functional abdominal pain (from 3.1% at 1 month to 12.5% at 6 months) and IBS (from 9.4% at 1 month to 12.5% at 6 months), and other subtypes (functional dyspepsia and abdominal migraine) were diagnosed less frequently (both from 6.2% at 1 month to 3.1% at 6 months). At 6 months, AP-FGIDs were diagnosed in 6 of 21 (28.6%) children with viral infections and in 2 of 9 (22.2%) of those with bacterial infections.

Among the 15 children with FGIDs at 6 months, 5 children had no changes in subtypes of FGIDs at the different follow-up visits (3 functional constipation, 1 fecal incontinence, and 1 IBS), whereas 3 patients changed subtypes at each follow-up visit (1 from functional constipation at 1 month to functional abdominal pain at 3 months, to functional abdominal pain plus constipation at 6 months; another from functional abdominal pain at 1 and 3 months to IBS at 6 months; and the third one from IBS at 1 month, to functional abdominal pain at 3 months, to IBS plus fecal incontinence at 6 months). In 4 patients, FGIDs were not reported at 1 month but were first diagnosed at 3 months and persisted unchanged at 6 months (1 patient had functional abdominal pain plus constipation; another had functional abdominal pain; the remaining 2 patients had constipation); in the last 3 patients, FGIDs were reported only at 6 months: functional abdominal pain, functional dyspepsia, and IBS, respectively. Two patients had FGIDs at 1 month but no FGIDs at 3 and 6 months.

Discussion

This prospective cohort multicenter study was designed to investigate the occurrence of PI-FGIDs in children. Our data support the existence of PI-FGIDs in pediatrics, with most patients exhibiting a phenotype consistent with AP-FGIDs, mostly functional abdominal pain and IBS. Even though functional constipation was the most frequent FGID in our patients, only AP-FGIDs were diagnosed with increased frequency in the exposed group at subsequent control visits, achieving significant difference compared with controls at 6 months.

Acute diarrhea and FGIDs are among the most common pediatric conditions. The fact that acute diarrhea is more common in preschool children and FGIDs frequently manifest for the first time in school-age children results in many children presenting to the pediatrician with a history of a previous diarrhea and more chronic functional gastrointestinal symptoms of recent onset. Thus, without a carefully planned study, one could argue that there is not necessarily a causal link between the 2 events. The strengths of our study include the prospective design of the study, the microbiological confirmation of all exposed patients (children presenting with acute diarrhea usually do not require routine etiological investigation), the presence of a matched control group, and the use of a previously validated and standardized tool to diagnose FGIDs. An indication of the external validity of our study is that the prevalence of FGIDs (12.5%-15.6%) in our control group is similar to the prevalence of 13% for functional dyspepsia and IBS previously reported in another epidemiological study of Italian children.[15] We were not able to quantify eventual FGIDs rate in the exposed group before acute diarrhea because the questionnaire was first completed

Table II. FGIDs diagnosed in exposed group within 1 month and 3 and 6 months after an acute diarrhea

	FGIDs within 1 month from acute diarrhea, exposed % (M, F)	FGIDs 3 months after acute diarrhea, exposed % (M, F)	FGIDs 6 months after acute diarrhea, exposed % (M, F)
Functional constipation	15.7% (3M, 2F)	25% (5M, 3F)	15.7% (2M, 3F)
IBS	6.3% (2M)	3.1% (1M)	9.4% (2M, 1F)
Nonretentive fecal incontinence	3.1% (1F)	3.1% (1F)	3.1% (1F)
Functional dyspepsia	3.1% (1F)	3.1% (1F)	3.1% (1F)
Functional abdominal pain	3.1% (1F)	12.5% (2M, 2F)	6.2% (1M, 1F)
Aerophagia + Functional constipation	3.1% (1M)	-	-
Abdominal migraine	-	3.1% (1M)	-
IBS + abdominal migraine	3.1% (1M)	-	-
Functional dyspepsia + Abdominal migraine	3.1% (1F)	-	-
Functional abdominal pain + Functional constipation	-	3.1% (1M)	6.2% (1M, 1F)
IBS + nonretentive fecal incontinence	-	-	3.1% (1M)

F, female; *M*, male.

Table III. FGIDs diagnosed in unexposed group within 1 month from enrollment and 3 and 6 months later

	FGIDs within 1 month from enrollment, unexposed % (M, F)	FGIDs 3 months later, unexposed % (M, F)	FGIDs 6 months later, unexposed % (M, F)
Functional constipation	9.4% (2M, 1F)	9.4% (2M, 1F)	9.4% (2M, 1F)
IBS	-	3.1% (1F)	3.1% (1F)
Functional abdominal pain	-	3.1% (1M)	3.1% (1M)
Abdominal migraine	3.1% (1M)	-	-

after the infection. However, even if we have possibly included children with preexisting FGIDs, the increasing incidence of PI-FGIDs in the following 6 months and the significant different percentage of FGIDs between exposed and control groups already present within 1 month from infection minimize the potential for a bias.

Despite the convincing evidence of PI-FGIDs (mostly PI-IBS) in adults,[1-5] the pathogenic mechanism of PI-IBS is still not fully understood. Recently, increased intestinal permeability, altered motility, persistent intestinal inflammation characterized by increased numbers of T-lymphocytes and mast cells, genetic predisposition, smooth muscle hyperreactivity to acetylcholine, continuous antigenic exposure (bacterial, parasitic, or dietary), or molecular mimicry of foreign antigens have been suggested by different authors.[16-19]

In particular, it has been reported[19] that colonic mast cell infiltration and mediator release in proximity to mucosal innervation may contribute to abdominal pain perception in patients with IBS. Because mast cell mediators are known to alter enteric nervous system physiology and induce visceral hypersensitivity, their release in close proximity to colonic innervation suggests that these mediators contribute to the disturbed sensory-motor function of IBS. Moreover, some authors have hypothesized that mast cells may also lead to altered enteric neuron function in patients with constipation as a result of excessive segmental contractile colonic motor activity and these motor changes would ultimately induce slow colonic transit. The same mechanisms also may be responsible for the high occurrence of constipation in our patient and for the increased frequency of AP-FGIDs in the exposed group at subsequent control visits, achieving significant difference compared with controls at 6 months.

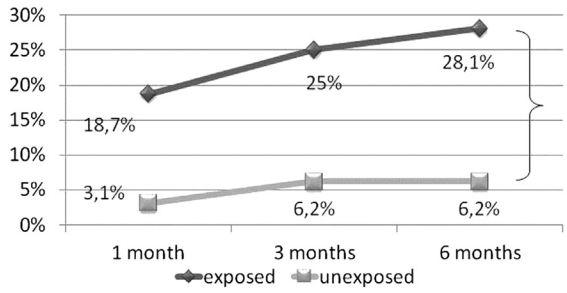

Figure 2. AP-FGIDs among exposed and unexposed patients. $P = .04$, relative risk = 1.7.

It is now well established that there is a close link between the neural and immunological networks within the gut and the central nervous system with continuous bidirectional communication, often referred to as the brain-gut axis. Evidence of dysbiosis in patients with IBS has been uncovered,[20] suggesting also an important role of the microbiota-gut-brain axis.[21-23] Insights into the interactions among enteric pathogens, the host epithelia, and the intestinal microflora are needed to improve our understanding of disease processes that may initiate IBS.[16]

Our study shows that, in children, both males and females have a similar risk of developing PI-FGIDs. This finding is in agreement with some adult literature showing a similar incidence of PI-IBS in both sexes[24-26] but contradicts the results of other studies (and a recent meta-analysis[5]) in which authors reported PI-IBS to be 3 times more frequent in women than in men.[24,27] In adults, the duration and severity of initial acute diarrhea were among the most important predictors of the development of PI-IBS.[5,24] In our study, we did not find any correlation between severity of acute diarrhea and frequency of FGIDs, and the exact duration of acute diarrhea was reported only in a minority of our study population not allowing an accurate analysis.

Another potential weakness of our investigation is the lack of stool studies in the control population to verify the absence of gastrointestinal pathogens, although no one in the control group reported diarrhea at recruitment. Moreover, undetected bacterial pathogens in this subgroup would have reduced (and not overestimated) the difference in the incidence of gastrointestinal symptoms compared with the exposed subjects. A further limitation of this study is the lack of information on psychological status and family dynamics, neither of which were evaluated. Both of these factors may play a role in the pathogenesis of FGIDs in children.[28-30]

Our group has previously found a significant increase in cases of FGIDs after acute bacterial gastrointestinal infections[6] but not rotavirus infections in children.[7] Conversely, in the current study, FGIDs occurred with a similar rate after bacterial and viral acute diarrhea, similarly to what was reported in a recent review in adults.[31] Among exposed children, AP-FGIDs (and particularly functional abdominal pain and IBS) were diagnosed with increased frequency at subsequent control visit, with significant difference, compared with controls, only at 6 months. These findings are consistent with adult data that have shown that IBS, in particular the diarrhea-predominant type, is the most common PI-FGID.[24,25,32]

If confirmed in future studies, our findings may have important implications. There are more than 200 million cases of diarrheal illnesses in the US each year, most of which occur in children.[33] Because acute diarrhea episodes are usually brief and self-limited illnesses, their long-term effects are rarely considered. Several investigators are showing a beneficial effect of probiotics and antibiotics in the treatment of gastrointestinal infections and FGIDs[34-37]; in adults,

probiotics have been claimed to be beneficial in IBS.[38] However, the effectiveness of antibiotics and probiotics for prevention of PI-IBS has not been established and should be carefully evaluated.

Our findings should be confirmed by larger prospective studies to better characterize the pediatric populations at greater risk for the development of PI-FGIDs in order to propose intervention strategies that could potentially minimize the development of PI-FGIDs. ■

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Appendix

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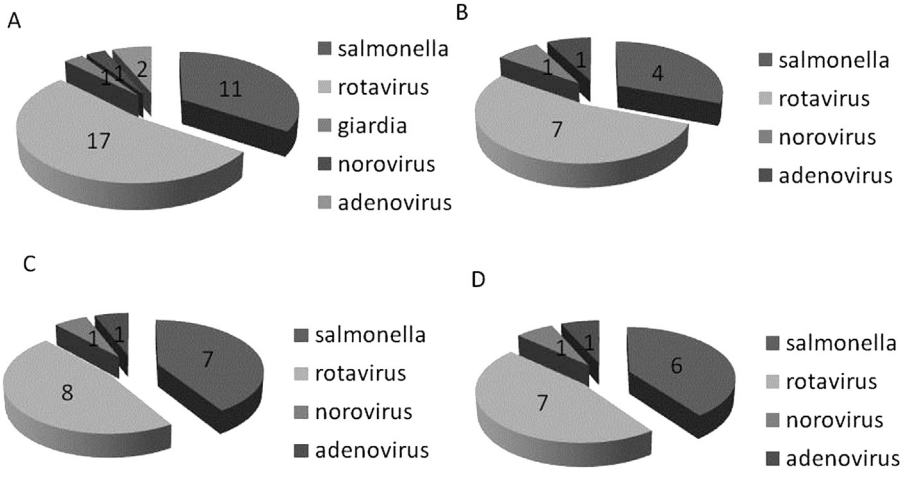

Figure 1. Etiology of acute diarrhea. **A,** Etiology of acute diarrhea in the exposed group. **B,** Etiology of acute diarrhea in children with FGIDs within 1 month from the acute diarrhea. **C,** Etiology of acute diarrhea in children with FGIDs at 3 months. **D,** Etiology of acute diarrhea in children with FGIDs at 6 months.