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