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Low Fecal Elastase: Potentially Related to Transient Small Bowel Damage Resulting from Enteric Pathogens

*Silvia Salvatore, †Sergio Finazzi, †Alessandra Barassi, *Mascia Verzelletti, *Anna Tosi, ‡Gian Vico Melzi d'Eril, *Luigi Nespoli

**Clinica Pediatrica Universitaria, Università dell'Insubria, Varese, Italy; †Laboratorio di Analisi Chimico-Cliniche, Ospedale di Circolo, Varese, Italy; ‡Dipartimento di Scienze Biologiche Sperimentali e Cliniche, Uiversità dell'Insubria, Varese, Italy*

ABSTRACT

Fecal elastase is considered to be a highly sensitive and specific non-invasive exocrine pancreatic function test. However, enteropathy may theoretically cause decreased exocrine pancreatic enzyme secretion through alteration of enteric hormone release.

Objective: The aim of this study was to evaluate the possible influence of transient small bowel damage on pancreatic elastase secretion.

Methods: We studied 166 children (aged 4 months to 14 years, mean 2 years); 114 of these children had acute enteritis and 52 children were control subjects (with gastro-intestinal symptoms or extra-intestinal diseases). Feces were collected from each patient 3 days after the onset of diarrhea and then tested for fecal elastase, bacterial pathogens, Rotavirus, and Adenovirus. Liquid fecal samples were not considered eligible for elastase measurement. Pancreatic elastase was measured using an ELISA method (Sche.Bo.Tech, Germany). We classified the results, expressed in μg/g stool, as: severe pancreatic insufficiency (<100 μg/g), moderate pancreatic insufficiency (100 to 200 μg/g), and normal (>200 μg/g).

Results: In the acute enteritis group we found severe levels in 14 (12%) children, moderate levels in 18 children (16%), and normal levels in 82 children (72%). In contrast, 52 of 52 (100%) control subjects demonstrated normal results. Statistical analysis (Wilcoxon rank test) demonstrated a significant difference between the enteritis and control groups ($P < 0.01$). Serial measurement of fecal elastase performed in 10 patients with enteritis showed a progressive increase of levels in 6 patients and an early decline with subsequent increases in the other 4 patients.

Conclusions: Transient exocrine pancreatic insufficiency may be present in transient small bowel disease, caused by both bacterial and viral infections, possibly related to reduced enteric CCK secretion. ***JPGN 36:392–396, 2003.*** **Key Words:** Fecal elastase—small bowel—enteritis—pancreatic function test—CCK. © 2003 Lippincott Williams & Wilkins, Inc.

INTRODUCTION

Fecal elastase (FE) is considered to be a highly sensitive and specific exocrine pancreatic function test. It is more sensitive than chymotrypsin for severe, moderate, and mild pancreatic insufficiency (1,2). Pancreatic elastase is not degraded during intestinal transit and thereby FE reflects exocrine pancreatic function (1,2). Several reports show its utility in cystic fibrosis with pancreatic involvement (3–7) and chronic pancreatitis in adults (8,9). In celiac disease its level seems inversely related to the degree of enteropathy with restoration of normal value when healing of mucosal damage occurs (10). In our study we evaluated the influence of transient small bowel damage, caused by infection, on FE.

Address correspondence to Silvia Salvatore, Cliinica Pediatrica, Ospedale F. Del Ponte, Via F. Del Ponte 19, 21100 Varese, Italy (e-mail: silvisa@tin.it).

MATERIALS AND METHODS

We sampled 166 patients (range 4 months–14 years, mean age 2 years) admitted to our hospital; 114 of these patients were admitted for acute enteritis and there were 52 control subjects (e.g., respiratory disease, functional abdominal pain, failure to thrive, and Toddler's diarrhea). Feces were collected from each patient at least 48 hours after the onset of diarrhea and tested for fecal elastase, bacterial pathogens, Rotavirus, and Adenovirus. In the last 10 consecutive patients recruited, serial measurements of FE were performed on the 3rd, 7th, 10th, and 15th day of diarrhea. As dilution of FE (stool water content >85%) occurs in diarrhea and causes false low results (11,12), liquid fecal samples were discarded from the study. All stool specimens were frozen at −20°C before analysis. FE was measured using the ELISA method according to the manufacturer's instructions (ScheBo.Tech, Germany). This measurement involved employing two binding monoclonal antibodies (IC 10A and II D 5F) to two distinct epitopes of FE. One hundred milligrams of stool were diluted 1:500 in sample wash buffer and the FE concentration (μg/g wet weight of stools) was mea-

sured photometrically. The manufacturers provide the following clinical ranges: severe pancreatic insufficiency (<100 μg/g), moderate pancreatic insufficiency (≥100≤200 μg/g), and normal (>200 μg/g). We decided to avoid any invasive and expensive pancreatic diagnostic procedures in our patients because of the self-limiting nature of the diseases.

For statistical analysis, because none of the data showed a gaussian distribution, a comparison of paired differences was performed with the Wilcoxon rank test. Differences with P values <0.01 were considered significant.

RESULTS

In the acute enteritis group (114 patients) we found severe FE levels in 14 patients (12%)(5 Rotavirus, 1 Adenovirus, 3 *Salmonella*, and 5 with non-identified pathogens), moderate levels in 18 patients (16%)(9 Rotavirus, 3 *Salmonella*, and 6 with non-identified pathogens), and normal levels in 82 patients (72%)(38 Rotavirus, 3 Adenovirus, 11 *Salmonella*, and 30 with non-identified pathogens) (Table 1; Fig. 1). Rotavirus was found in 52 (46%) patients with enteritis, Adenovirus in 4 patients (3.5%), *Salmonella* in 17 patients (15%) and no pathogens were identified in 41 patients (36%). Overall, the FE levels were compatible with severe or moderate pancreatic insufficiency in 32 (28%) of patients with acute enteritis. In contrast, 52 of 52 (100%) control subjects had normal results. In the 10 patients with infectious diarrhea who received follow-up evaluation, FE showed two different patterns. In 6 patients (2 Rotavirus, 3 *Salmonella*, 1 non-identified pathogens), FE showed a progressive increase with pathologic levels in 3 patients after 3 days and 2 patients after 7 days, with normalization of all patients in 10 days and a further increase by 15 days from the onset of diarrhea (Fig. 2a). In the other 4 patients (3 Rotavirus, 1 non-identified pathogens), we noticed normal levels at the first determination, but then decreased levels in the subsequent 2 follow-up samples. Pathologic FE levels and a concomitant increased number of stools were seen in 3 patients (2 Rotavirus and 1 non-identified pathogen) at 10 days from onset of diarrhea. This was followed by a subsequent increased FE levels with normalization of FE, by 15 days in 2 patients (Fig 2b). Neither the diet nor the severity of dehydration were significantly correlated with the values of FE. Serum amylase tested in patients with enteritis did not correlate with FE.

TABLE 1. *Results of fecal elastase in enteritis according to the different etiologies*

		Fecal elastase		
	n	<100 μg/g	100–200 μg/g	>200 μg/g
Rotavirus	52	5	9	38
Salmonella	17	3	3	11
Adenovirus	4	1	/	3
Nonidentified	41	5	6	30

Statistical analysis showed a significant difference between the enteritis and control groups ($P < 0.01$)(Fig. 3).

DISCUSSION

In our study we showed that FE may be severe or moderately abnormal in 28% of patients with infectious enteritis. Rotavirus and *Salmonella* were the most common identified pathogens (20/32, 62.5%) associated with pathologic FE levels. As all liquid fecal samples were discarded and normal results were found in patients with Toddler's diarrhea, we considered the possibility of false positive FE caused by dilution effect very unlikely. Serial measurements of FE showed pathologic levels 3 days after the onset of diarrhea in 3 children, after 1 week, in 2 of the 3, after 10 days in 3 different patients and after 2 weeks in 2 of the latter 3. Interestingly, the suspected enteropathy responsible for the decreased pancreatic secretion may take more than 15 days to recover as supported by pathologic level of follow-up FE determination in 2 patients with severe infectious enteritis caused by Rotavirus. Our finding of low FE in 27% of Rotavirus and 35% of *Salmonella* enteritis may reflect the presence of transient enteropathy in these patients. Although we did not perform biopsies in our patients because of the self-limiting disorders, our results are consistent with previous reports of subtotal villous atrophy in either Rotavirus or bacterial enteritis (EPEC, *Salmonella*) demonstrated in up to 50% of patients with protracted diarrhea (13,14).

Preliminary results of our study (15) had suggested the hypothesis that decreased release of CCK by the damaged intestinal mucosa, even due to a transient infectious event, could be responsible for low FE results. This speculation has been recently supported, in 6 patients with enteropathy and FE pathologic levels, by restoration of normal pancreatic enzyme levels after secretin-CCK test (16). These findings provided evidence of the secondary origin of pancreatic insufficiency in patients with enteropathy (due to a reduction of pancreatic stimulation by the inflamed intestine) with normal pancreatic secretory capacity and response to appropriate humoral stimuli. In the same study, a highly significant correlation between duodenal morphology and inflammation and levels of FE has been shown in different enteropathies (16).

FE is considered to be an excellent non-invasive marker of exocrine pancreatic function. The sensitivity and specificity of FE is greater than 90% for moderate and severe exocrine pancreatic insufficiency, clearly superior to fecal chymotrypsin (1–3,6,8,9,12,17). It is also simple, relatively cheap, stable (5), with very low intra-individual variation (1,2,18). A significant correlation exists between FE and stimulated duodenal volume, and the bicarbonate, amylase, lipase, and trypsin concentration of duodenal aspirates (1,2,6,9). In normal condi-

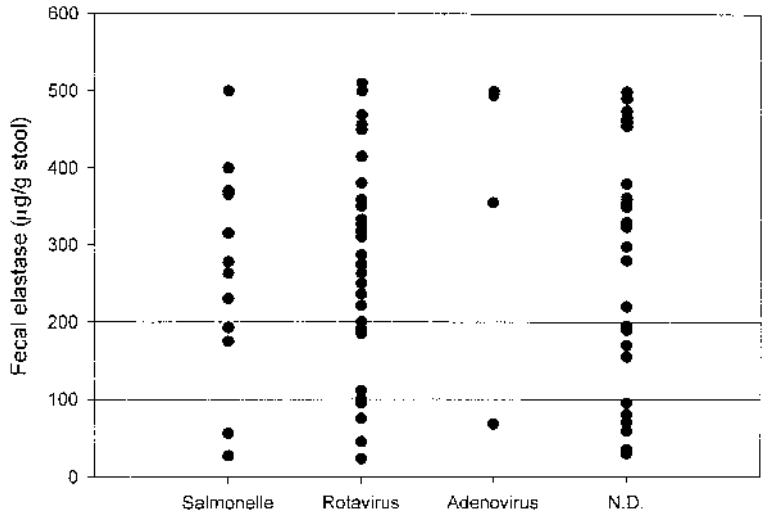

FIG. 1. Fecal elastase levels according to different enteric pathogens in acute enteritis.

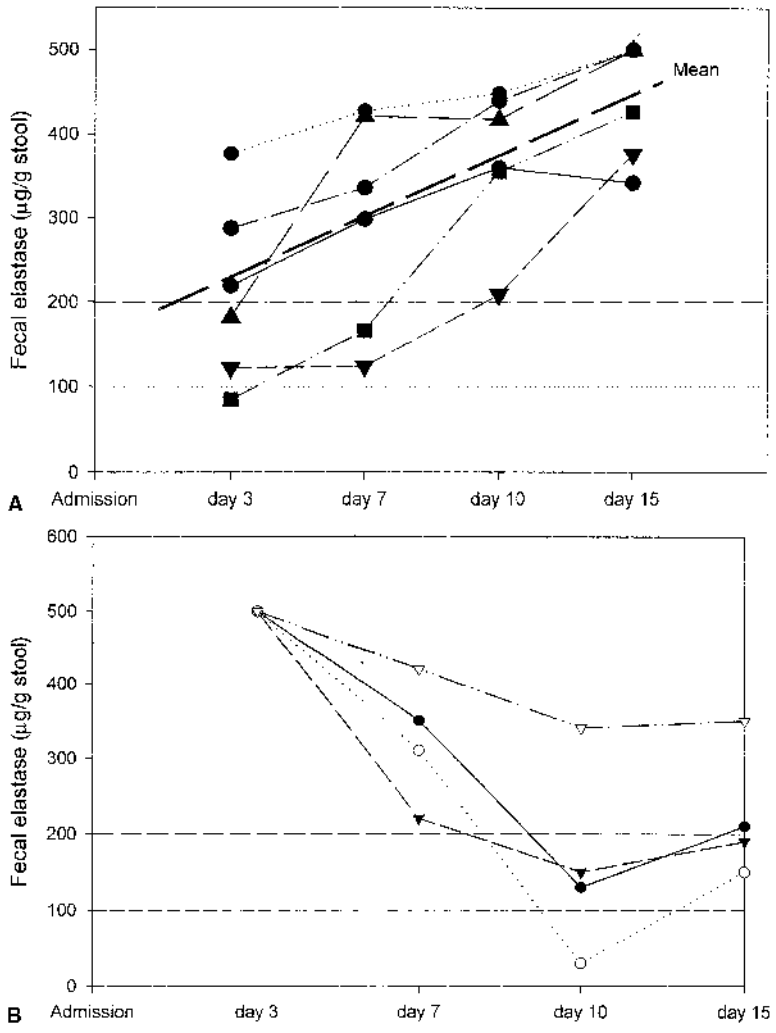

FIG. 2. (A) Serial measurement of fecal elastase in 6 patients with enteritis. (B) Serial measurement of fecal elastase in 4 patients with enteritis.

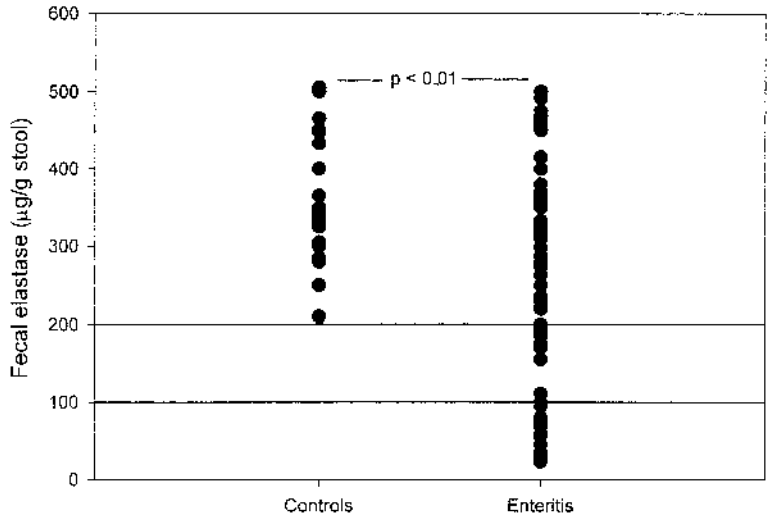

FIG. 3. Fecal elastase levels between enteritis and control group.

tions, both neural (entero-pancreatic, cholinergic, vago-vagal reflexes) and hormonal (cholecystokinin) pathways mediate the pancreatic enzyme response to intestinal stimulants. CCK seems to be the major mediator of the response to high loads of amino acids and fatty acids (19). Immuno-histochemistry identified approximately 1650 CCK cells per cross-section in the duodenum of humans (20) and jejunal mucosal integrity is necessary for the normal secretion of enteric hormones by the respective cells located in the small bowel mucosa (10). The close link between the small bowel mucosa and the exocrine function of the pancreas is highlighted in celiac disease. In 10 of 30 celiacs (33%) FE was subnormal at diagnosis. After 2 months of gluten-free diet, FE deficiency persisted in only 2 patients, possibly related to a more severe enteropathy (21), and independent of nutritional status (22). Recently, FE was found to be inversely related to the degree of intestinal damage in celiac disease, emphasizing the role of gluten-related mucosal damage on abnormal secretion of pancreatic enzymes, related possibly to reduced hormonal signaling (10). In celiacs pancreatic impairment has been associated with CCK abnormalities (23–25) and is clearly a reversible phenomenon as it recovers with gluten-free diet (26,27) and restoration of the mucosa (10).

In recent years, a few patients with different malabsorption diseases (celiac disease, *Giardiasis*, cow-milk sensitive enteropathy, Crohn disease, and small bowel syndromes) showed low FE at diagnosis and normalization of FE with restoration of small bowel integrity. This data further supports the close relationship between decreased FE and enteropathy regardless of the underlying diseases (4,16,17,28–30).

In conclusion, low FE and transient exocrine pancreatic insufficiency may be present in infectious enteropathy, possibly related to reduced enteric CCK secretion. As the specificity of FE in differentiation between "primary" exocrine pancreatic insufficiency and intestinal malabsorption seems rather poor (30), persisting pathologic FE could reflect morphologic and functional derangements of the small bowel mucosa and could indicate further investigation to exclude underlying enteropathy. As dilution effect (stool water content >85%) may account for false positive FE results (11,12), liquid fecal samples should not be used for FE determination. If only watery stools are available, lyophilization of the feces should be performed (11).

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Clinical Quiz, continued from page 375

ANSWER: MESENCHYMAL HAMARTOMA

Mesenchymal hamartoma (MH) is a benign liver tumor and accounts for 18% to 29% of these tumors (1). MH of the liver is usually seen in children in the first 2 years of life. The tumor consists of a solid component and multiple cysts of various sizes, filled with clear fluid and mucoid material. Without treatment, these lesions can grow to an enormous size. (In our child the tumor involved the right lobe and the weight was 2.5 Kg (Fig. 2: histopathologic section)) and may cause severe displacement of the diaphragm. Treatments included marsupialization, simple excision, partial hepatectomy, and orthotopic liver transplantation (2). Recurrence of the tumor after marsupialization or partial excision could be explained by the hypothesis of Lennington et al. (3). According to this report, recurrence is caused by remnants of the solid part of the tumor or the underlying vascular anomaly of the hamartoma. Another risk of partial resection may be the development of a malignant tumor; this occurrence has been reported only twice (4,5). The best treatment of MH of the liver is a complete excision by enucleation or by partial hepatectomy, because incomplete excision often results in recurrence and operative risk of enucleation or partial hepatectomy are low. In unresectable cases of MH, a liver transplantation might be considered as an option. In our patient, a complete excision of the tumor was performed by extended right hemihepatectomy. The postoperative course was uneventful. Seven years after surgery, the boy is in good health and ultrasonographic scan showed no recurrence.

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