Chronic pancreatitis is associated with a high prevalence of giardiasis

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JJ LOPEZ, JA WRIGHT, RA HAMMER, A ERTAN. Chronic pancreatitis is associated with a high prevalence of giardiasis. *Can J Gastroenterol* 1992;6(2):73-76. In a previous study, a significantly higher prevalence of giardiasis was found in patients with cystic fibrosis compared with a control population (28.0 versus 6.3%, $P < 0.0006$). In this study, the prevalence of giardiasis in an adult population with chronic pancreatitis was investigated. The test population consisted of 15 patients with alcoholic pancreatitis and 50 volunteers with hypertension or orthopedic problems who were surveyed for *Giardia lamblia* by counterimmunoelectrophoresis (CIE) in fecal samples. CIE results were positive in four of 15 patients (27%) with chronic pancreatitis and negative in all control subjects ($P < 0.001$). It was concluded that patients with chronic pancreatitis, similar to patients with cystic fibrosis, have a previously unrecognized increased prevalence of giardiasis compared with a control population. It is important to investigate for *G lamblia* in any patient with pancreatic insufficiency whose diarrhea is difficult to control by dietary measures or pancreatic enzyme supplementation.

Key Words: Chronic pancreatitis, Diarrhea, Giardiasis

La pancréatite chronique est associée à une prévalence élevée de giardiase

RESUME: Une étude précédente notait une prévalence significativement plus élevée de giardiase parmi les patients porteurs de fibrose kystique que dans une population témoin (28 c. 6,3 % $P < 0,0006$). Dans le présent article, les auteurs ont examiné la prévalence de giardiase dans une population de sujets adultes atteints de pancréatite chronique. La population étudiée comptait 15 patients souffrant d'une pancréatite alcoolique et 50 volontaires hypertendus ou présentant des problèmes orthopédiques. Les échantillons de fèces de tous les sujets ont été soumis à une contre-immunoélectrophorèse à la recherche de *Giardia lamblia*. On a relevé des résultats positifs chez quatre des quinze patients

GIARDIA LAMBLIA IS A FLAGELLATED enteric protozoan which has been contracted in every part of the world and is an important cause of endemic and epidemic diarrhea. The prevalence of *G lamblia* ranges from 1 to 20% and varies with socioeconomic level and age (1). In the United States, approximately 4% of the population harbour the organism, making it the most prevalent enteric parasite and the leading infectious agent identified in water-borne outbreaks of diarrhea. Between 1965 and 1984, 90 separate outbreaks affecting over 23,000 people were reported (2,3).

Patients with symptomatic giardiasis often complain of acute or chronic diarrhea, weight loss and diffuse or epigastric abdominal pain (which often is exacerbated by eating and varying degrees of malabsorption symptoms) (4). These symptoms are similar to those frequently encountered in patients with chronic pancreatitis (5); although an association between these two diseases has been suspected (6), there has been no systematic investigation of a potential association. In a recent study, an increased prevalence of giardiasis was found in a group of patients with cystic fibrosis, all of whom had pancreatic exocrine insufficiency (7). Subsequently, the authors proceeded to investigate the preva-

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atteints de pancréatite chronique (27%), et négatifs chez tous les sujets témoins ($P < 0.001$). On conclut que l'augmentation de la prévalence de giardiose par rapport au groupe témoin n'était jusque-là pas reconnue chez les patients atteints de pancréatite chronique, comme chez les patients porteurs de fibrose kystique. Il est important de rechercher *G lamblia* chez tout insuffisant pancréatique dont les diarrhées restent rebelles à des mesures d'hygiène alimentaire ou à un apport complémentaire d'enzymes pancréatiques.

lence of giardiasis in an adult population with chronic pancreatitis and assess the effect of treatment on their symptoms.

PATIENTS AND METHODS

Fifteen patients (13 male, two female) aged 33 to 73 years (mean 50.4) suffering from alcohol-induced end-stage chronic pancreatitis were selected. The diagnosis of chronic pancreatitis was established by results of plain radiographs of the abdomen, endoscopic retrograde cholangiopancreatography, computed tomography scan of the abdomen, secretin test and/or the Bentiromide test (Table 1). No patient was diagnosed as having chronic pancreatitis based only on the Bentiromide test.

All of the patients with chronic pancreatitis had steatorrhea and were receiving pancreatic enzyme supplementation. Nine of these patients had evidence of weight loss, diarrhea and postprandial abdominal pain for at least six months, and had failed to respond to conventional medical management for chronic pancreatitis. In these patients, the degree of weight loss ranged from 4.5 to 11 kg (mean net loss 7.4) and their diarrhea consisted of four to six bowel movements per day with production of foul-smelling stools. Sudan III stain demonstrated fat globules.

The control population consisted of 50 volunteers (42 male, eight female) aged 29 to 76 years (mean 48.9) from the same hospital population as the study group. They were being treated for uncomplicated hypertension or orthopedic problems and had no evidence of alcoholism, pancreatic disease or other medical illness discernible by history and medical chart review. All participants in the study were residents of Louisiana and had not traveled out-

side the state during the past six months. They did not have any conditions known to predispose them to giardiasis, including homosexuality, cystic fibrosis or immunoglobulin deficiency syndromes (7-9).

Detection of *G lamblia* was accomplished by collecting a single stool specimen and testing it by counterimmunoelectrophoresis (CIE) for the presence of *G lamblia* surface antigens; these antigens are present on cysts and trophozoites (10). Ten microlitres of liquified stool was placed on the cathode end of an electrophoresis gel plate. The anode end contained rabbit immunoglobulin (Ig) G and IgM from animals immunized with a purified preparation of *G lamblia* cysts. A constant potential (220 V) was applied for 30 mins, and the plates were examined for precipitation bands after 24 and 48 h of incubation at 4°C. The presence of a precipitation band was considered diagnostic for *G lamblia*. Each stool specimen was tested twice. This CIE assay has been shown previously to be more sensitive than direct examination of stool and duodenal fluid, and has a sensitivity and specificity for detection of *G lamblia* greater than 95% (10).

Statistical analysis of the results was made using the Fisher-exact test. $P < 0.05$ was considered statistically significant.

RESULTS

G lamblia was detected in four of 15 patients (27%) with well-documented chronic pancreatitis (Table 1). None of the control subjects had evidence of giardiasis by CIE. The higher rate of giardiasis in the patients with chronic pancreatitis was statistically significant ($P < 0.001$). The four patients who tested positive were among those who had evidence of weight loss, steatorrhea

and postprandial abdominal pain (Table 1); these four had worsening symptoms which could not be controlled with increasing pancreatic enzyme supplementation, bicarbonate or histamine-2 receptor antagonists. The patients with positive results received a one-week course of antibiotic therapy for giardiasis (oral metronidazole 250 mg three times a day for seven days) without change in any other medication. Following treatment, they reported complete resolution of their diarrhea and abdominal pain, and CIE retesting of their stools revealed clearing of *G lamblia*.

DISCUSSION

In the current study, the prevalence of giardiasis in an adult population with alcohol-induced chronic pancreatitis was 27%. Although the study group size was small, the prevalence rate is similar to the 28% for giardiasis found in larger groups of patients with cystic fibrosis, all of whom had pancreatic exocrine insufficiency (7). Combined consideration of the results from these two studies supports the hypothesis that pancreatic exocrine insufficiency may be a predisposing condition to intestinal colonization with *G lamblia* and suggests pancreatic exocrine secretion may have a role in host defense against *G lamblia*. The possible mechanisms by which pancreatic exocrine insufficiency may predispose patients to giardiasis include deficiency of pancreatic enzymes, decreased pancreatic bicarbonate secretion and absence of nonimmunological factors with antimicrobial activity normally present in pancreatic juice.

G lamblia, like some bacteria and other protozoa, has lectin activity associated with its surface membrane which has a high specificity for D-glycosyl and D-mannosyl residues (11, 12). This surface membrane lectin activity mediates giardia trophozoite adherence to intestinal epithelial cells with preference to those in the small intestine. Trypsin removes parasite surface lectin and possibly other surface determinants involved with parasite attachment to enterocytes, and may also mediate parasite release from the gut

TABLE 1
Clinical data in 15 patients with chronic pancreatitis. First four patients had positive counterimmunoelectrophoresis for *Giardia lamblia* in their fecal samples

Case	Age	Sex	CP duration since diagnosis (years)	Diarrhea and weight loss	Pancreatic calcification by plain abdominal radiographs	Abnormal computed axial tomography scan*	Abnormal ERCP†	Abnormal secretin test‡
1	36	M	2	+	—		+	+
2	38	M	>5	+	±	+	+	
3	52	M	3	+	+	+		+
4	65	M	4	+	+	+		
5	33	M	2	+	—		+	+
6	38	M	<1	—	—		+	
7	40	M	8	+	+	±	—	+
8	42	F	3	—	—	+	±	
9	47	M	2	—	—	+		+
10	50	M	5	+	+			
11	53	F	7	+	—	+		+
12	56	M	4	—	—	+	+	
13	58	M	Undetermined	+	+		+	
14	65	M	<10	—	+	+	+	
15	73	M	24	—	+	+	+	

CP Chronic pancreatitis; ERCP Endoscopic retrograde cholangiopancreatography; *Enlarged pancreatic duct, calcification and/or calculi; †Pancreatic duct dilation, irregularity, stricture and/or ductal calculi; ‡Volume <2 mL/kg/h and bicarbonate concentrations <70 mEq/L after intravenous secretin (1 u/kg) stimulation

epithelium (11). In the absence or deficiency of tryptic activity, ability of *G lamblia* to attach to enterocytes may be enhanced.

G lamblia trophozoites can be killed in vitro by normal human duodenal and upper jejunal fluid. This effect has been attributed, in part, to products of lipolysis including unsaturated fatty acids, monoglycerides and lysophospholipids (13). In humans, lipid is digested by a number of lipases including pancreatic triacylglycerol lipase, carboxylester hydrolase and phospholipases A and B (14). The concentration of lipolytic products in intestinal fluid is dependent greatly on their relative rates of production which, in turn, directly is related to the secretion and availability of lipolytic enzymes and consumption of fat. In the absence of these enzymes, the lipolytic effect would be missing – thereby removing a potential defense against intestinal colonization by *G lamblia*.

The activity of pancreatic enzymes, both proteolytic and lipolytic, is pH-sensitive. Whenever the duodenal pH falls below 4, these enzymes become irreversibly inactivated. In patients with chronic pancreatitis who have steatorrhea, bicarbonate secretion is reduced markedly, and there is impaired

ability to neutralize even small loads of acid in the duodenum (15). Consequently, the intraluminal duodenal pH tends to be lower than 4, rising to between 5 and 6 only during the early postprandial period (16). The abnormally low duodenal pH inactivates both lipolytic and proteolytic activity of pancreatic enzymes, thereby neutralizing the antimicrobial defence they normally would confer.

Within human pancreatic juice there is an antimicrobial factor which is pH-dependent; its activity is optimal at pH 8.5 but it is inactive when the pH drops to 7.0 or lower (17) and would, therefore, be active within the range of pH found in normal pancreatic secretions (18). The factor is heat stable, has been found to be bactericidal for enterobacteriaceae, bacteriostatic for *Pneumocystis aeruginosa* and staphylococci, and fungistatic against *Candida albicans* (17). It is not an enzyme, immunoglobulin or complement factor.

It is quite possible this factor (or other similar factors still unidentified in pancreatic juice) also are active against protozoa, including *G lamblia*. In patients with pancreatic exocrine insufficiency, one would expect both a deficiency of the factor(s) and complete loss of its activity in the duodenal

lumen due to the lower pH of the intraluminal contents.

The authors' study reveals that it is important to investigate for *G lamblia* in any patient with pancreatic exocrine insufficiency whenever their symptoms are difficult to control by dietary and pancreatic enzyme measures. If left unrecognized, giardiasis superimposed on chronic pancreatic exocrine insufficiency may result in increased diarrhea and weight loss beyond that expected for the degree of pre-existing pancreatic disease.

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