Benign pancreatic hyperenzymemia (Gullo syndrome), histamine intolerance, and carbohydrate malabsorption

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Benign pancreatic hyperenzymemia (Gullo syndrome) is characterized by a more than threefold increase of the pancreatic enzymes lipase and amylase in the absence of a pancreatic disease over a period of more than 1 year, with elevations and significant undulations of pancreatic enzyme serum concentrations occurring on a day-to-day basis for 5 consecutive days. Nonspecific abdominal complaints may be caused by carbohydrate and/or protein malabsorption. We report a patient with benign pancreatic hyperenzymemia with lactose and histamine malabsorption; the symptoms of gastrointestinal malabsorption were treated successfully with an individually tailored lactose- and histamine-free diet.

Benign pancreatic hyperenzymemia (Gullo syndrome) is characterized by a more than threefold increase of the serum pancreatic enzymes lipase and amylase in the absence of a pancreatic disease (1). Gastrointestinal malabsorption is caused mainly by carbohydrates (lactose and fructose), proteins (gluten), and biogenic amines (e.g., histamine) and frequently manifests in nonspecific abdominal complaints. We tested a patient with Gullo syndrome for gastrointestinal malabsorption and diagnosed lactose and histamine malabsorption. This patient with nonspecific abdominal complaints due to lactose and histamine malabsorption recovered with an individually tailored diet free of lactose and histamine within a few days (2).

CASE DISCUSSION

A 71-year-old white man was examined for repeatedly elevated lipase and amylase serum values over a time period of 3 years and presented with sustained nonspecific abdominal complaints. His symptoms were postprandial abdominal discomfort in the right upper quadrant, bloating, diffuse abdominal pain, and semisolid stools. Physical examination showed a bloated abdomen, and anamnesis revealed no weight loss.

During the 3 years before presentation, the elevation of serum lipase and amylase levels reached 450 U/L (normal <60) and 367 U/L (normal 20–100), respectively. Abdominal sonography revealed gallbladder stones, and subsequently a laparoscopic cholecystectomy was performed. Repetitive abdominal computed tomography and magnetic resonance imaging demonstrated no abdominal or pancreatic abnormalities. Gastroscopy ruled out *Helicobacter pylori* infection or other abnormalities, and colonoscopy disclosed no abnormalities. The serum total cholesterol was 253 mg/dL; low-density lipoprotein cholesterol, 166 mg/dL; glutamate-oxaloacetate-transaminase, 49 U/L (normal <35); and glutamate-pyruvate-transaminase, 52 U/L (normal <45). Using a radio extraction assay, the diamine oxidase in serum (Sciotec Diagnostic Technologies, Tulln, Austria) was 2.6 U/mL (normal >10 U/mL) (3). Triglycerides, calcium, IgG4, carcinoembryonic antigen, carbohydrate antigen 19-9, fecal pancreatic elastase test, and C-reactive protein were normal. The erythrocyte sedimentation rate was <20 mm in 2 hours.

Hydrogen breath tests were performed to detect lactose and fructose malabsorption (Gastrolyzer, Bedfont Scientific Inc., Kent, England). During the breath test with a drink containing 50 g lactose dissolved in 200 mL water, the end-expiratory exhalation of hydrogen was measured every 30 minutes for a period of 150 minutes. The hydrogen value increased from the baseline 10 up to 19 parts per million (ppm) (normal <20). This test demonstrated decreasing blood glucose levels from a fasting value of 105 mg/dL to 88 and 86 mg/dL after 1 and 2 hours, respectively (normal is an increase >20) (4). In the breath test with a drink containing 25 g fructose load dissolved in 200 mL of water, the end-expiratory exhalation of hydrogen was <20 ppm. Antibodies against tissue transglutaminase were not found.

A registered dietitian developed an individually tailored diet for this patient, which resulted in the improvement of symptoms within a few days. At 6 months, the patient was still symptom free. Written informed consent was obtained for all procedures, which were in accordance with the Declaration of Helsinki and the recommendations of the local ethics committee.

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Table. Quantitative photometric determination (Cobas Roche) of serum lipase and amylase values during 5 consecutive days

Test	Normal value	Day 1	2	3	4	5
Lipase (U/L)	0–60	211	276	187	215	518
Amylase (U/L)	20–100	210	230	196	202	260

DISCUSSION

Guidelines for diagnosis of pancreatitis are based on the presence of two of the three following criteria: typical abdominal pain, characteristic imaging findings, and elevated lipase and/or amylase levels of threefold or higher than the upper limit of normal (5). However, high amylase and/or lipase levels do not automatically confirm the diagnosis because there are numerous differential diagnoses, including renal insufficiency, inflammatory bowel disease, pathologies of the hepatobiliary tract system, neoplastic diseases, diabetes mellitus, drugs, and infections (6). Diagnosis of Gullo syndrome is made if all evaluations for pancreatic diseases are normal during the time period of at least 1 year, and if elevations and significant undulations of pancreatic enzyme serum concentrations occur on a day-to-day basis for 5 consecutive days *(Table)* (7). It is speculated that a defect in the intracellular transport of pancreatic enzymes in exocrine pancreatic cells may be responsible for the increased passage of enzymes into the blood circulation (8).

However, if certain foods consumed before the tests might influence enzyme levels, it was reported that the ingestion of various meals did not increase pancreatic enzymes (1). Since in our patient lactose- or histamine-rich or -reduced food did not influence enzyme levels, we confirmed this conclusion. The clinical importance in asymptomatic individuals with Gullo syndrome is to differentiate a myriad of differential diagnoses, and multiple complex diagnostic tests and/or hospital admissions may be prevented (7).

Gastrointestinal malabsorption syndromes are caused by carbohydrates (mainly lactose and fructose), proteins (gluten), and biogenic amines (e.g., histamine). Unabsorbed food results in symptoms due to bacterial metabolism and fermentation in the colon. Various combinations of malabsorption were reported in patients with gastrointestinal malabsorption syndromes (2).

Lactose malabsorption is related to lactase deficiency and causes nonspecific gastrointestinal complaints with the ingestion of dairy products (9). Histamine intolerance is a disproportionate amount of histamine in the body caused by the consumption of histamine-containing food and/or a reduced ability of diamine oxidase to catalyze histamine within the gastrointestinal tract. In the patient described here, the diagnosis of this condition was based on a diamine oxidase value <10 U/mL in serum and more than two typical gastrointestinal symptoms allegedly belonging to histamine malabsorption (10). Nonspecific abdominal symptoms in this patient with benign pancreatic hyperenzymemia (Gullo syndrome) were due to lactose and/or histamine malabsorption and were treated effectively with an individually tailored diet.

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