



Case Report

Healthy Chinese with benign pancreatic hyperenzymemia

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Abstract

Benign pancreatic hyperenzymemia, or Gullo's syndrome, is an uncommon syndrome characterized by a long-term increase of serum pancreatic enzyme in the absence of pancreatic diseases. It is primarily discovered incidentally and occurs in either sporadic or familial form. Herein, we report the first case of benign pancreatic hyperenzymemia in Taiwan. A 57-year-old Chinese male was incidentally noted with elevated serum amylase and lipase levels during a health check-up and was diagnosed with benign pancreatic hyperenzymemia using a series of image and serological tests. Although this is the first case of benign pancreatic hyperenzymemia in Taiwan, its prevalence may be underestimated due to the diagnostic difficulties. Correct diagnosis of this disease is important to avoid costly test duplication, unfounded anxieties, and multiple consultations.

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1. Introduction

An elevation of serum pancreatic enzymes is a well-known manifestation of various pancreatic and nonpancreatic diseases.^{1–3} The most common etiologies are acute pancreatitis and pancreatic neoplasms. Such elevated levels may be also associated with diseases of the pancreatic endocrine or ducts, such as diabetic ketoacidosis.⁴ There are also other non-pancreatic etiologies such as ectopic pregnancy, mumps,

human immunodeficiency virus infection, macroamylasemia, head trauma, acute cholecystitis, hypertriglyceridemia, intestinal infarction, duodenal ulcer, obstruction or inflammatory bowel disorders, liver diseases, abdominal trauma, and renal insufficiency.³

In 1996, Gullo^{1,2} reported a new syndrome called benign pancreatic hyperenzymemia, which was also named Gullo's syndrome. It is characterized by serum pancreatic enzyme elevations in the absence of pancreatic disease and occurs either sporadically or genetically. Because of its asymptomatic presentation, it is mostly discovered incidentally.

Increased levels of pancreatic enzymes may be secondary to an imbalance between pancreatic release and renal clearance. In the absence of pathologies of the pancreas, the possible causes of an increased enzyme release from the

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pancreas are an obstruction of the pancreatic duct system (generally mild or direct acinar cell damage) which in turn alters the normal exocytosis process in acinar cells.³

Although the etiology of benign pancreatic hyperenzymia is unclear, the pathological mechanism is probably related to a defect in the basolateral surface of acinar cells to secrete enzymes, which may result in the increased passage of enzymes into the bloodstream.¹ It may also be caused by changes in the duct of Wirsung by secretin stimulation.⁵

It is crucial to obtain a careful evaluation of the patient's clinical history, including family history regarding familial pancreatic hyperenzymia⁵ (when the patient has at least one family member with the same enzyme anomaly), drug use³ (such as paracetamol, steroids, ephedrine, and chemotherapy), and symptoms to establish the diagnosis of benign pancreatic hyperenzymia.⁶ In patients with nonspecific biochemical alteration, the possible causes should be carefully investigated.

The exact incidence of benign pancreatic hyperenzymia is not known nor is that of the more familiar hyperenzymia. A search from PubMed detected about 24 articles that made reference to benign pancreatic hyperenzymia. In those articles, most of the study groups were Italian, with a few involving other countries. This is an uncommon syndrome, especially in Asian countries, and it may be underestimated due to its difficulty of diagnosis. Herein, we report a healthy Chinese case of benign pancreatic hyperenzymia presenting with asymptomatic pancreatic hyperenzymia.

2. Case report

A 57-year-old Chinese man was informed that he had high levels of serum amylase and lipase during a health check-up in the United States 1 year previously, after which he then visited our outpatient Department of Gastroenterology for a diagnostic work-up in March, 2012. He denied any symptoms and related that all of his family members are in good health status. He denied use of alcohol, smoking, or any exposure history to hepatotoxic agents. He had received the following tests including serum creatinine, serum amylase, amylase iso-enzymes, lipase, alanine and aspartate transaminases, alkaline phosphatase, gamma-glutamyl transpeptidase, serum albumin and gamma globulins, prothrombin time, iron, transferrin, and ferritin folic acid, vitamin B12, hepatitis viral serology, serum cholesterol 184 mg/dL (normal range <200 mg/dL), and serum triglyceride 160 mg/dL (normal range 50–200 mg/dL). They were all within normal range except hyperamylasemia 330 U/L (normal range 28–100 U/L) and hyperlipasemia 619 U/L (normal range 22–51 U/L) (Fig. 1). A series of image studies including abdominal ultrasound, abdominal computed tomography (CT), and magnetic retrograde cholangiopancreatography (MRCP) all revealed normal findings (Fig. 2). Therefore, serum amylase and lipase levels were followed regularly, and no symptoms occurred nor were any physical abnormality detected during the follow-up periods. Finally, this patient was diagnosed with benign pancreatic hyperenzymia after an observation period of about 2 years

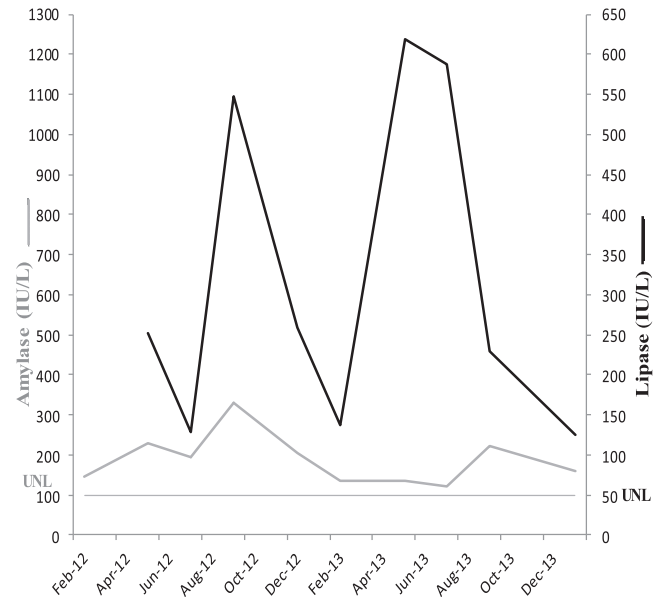


Fig. 1. Serial follow-up of serum amylase and lipase levels in a Chinese male. UNL = upper normal limit.

without symptoms of pancreatic diseases or structural changes.

3. Discussion

Pancreatic hyperenzymia is common in pancreatic diseases and also occurs in nonpancreatic etiologies such as renal failure, brain trauma, traumatic shock, postoperative diabetic acidosis, renal transplants, pneumonia, pregnancy, and macroamylasemia.^{3,7} However, elevated pancreatic enzymes could be a nonspecific phenomenon without any clinical implication.⁸ To make a diagnosis of benign pancreatic hyperenzymia, clinical physicians should thoroughly investigate the patient's clinical history including drug and family history to assess other possible causes.

Patients with benign pancreatic hyperenzymia^{1,4,9} are diagnosed mostly by excluding pancreatic abnormalities with repeated ultrasonography. Other advances through imaging such as CT, endoscopic retrograde cholangiopancreatography, and MRCP have also been applied in several studies.^{8,10} It was shown that 89 out of a total of 100 individuals indicated normal ductal findings after a series of image studies (Table 1).¹¹ Only 11% of patients had pathologic findings including ductal dilatation and/or irregularity, pancreas divisum, small cysts, intraductal papillary mucinous tumors, and sphincter of Oddi dysfunction. If asymptomatic patients are noted with increased pancreatic enzymes lasting for more than 2 years and negative findings with thorough imaging tests (pancreatic CT scan and/or MRCP), benign pancreatic hyperenzymia could be diagnosed. Nevertheless, although it is rare, previous studies demonstrated that 1–2% of benign pancreatic hyperenzymia cases might be the first clue for pancreatic malignancy.¹

In the study by Gullo et al,¹¹ a total of 207 patients with asymptomatic hyperenzymia were followed up for 5 years.

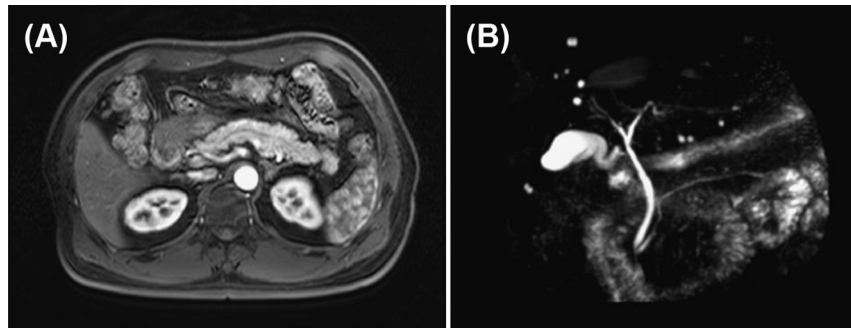


Fig. 2. (A) Magnetic resonance image; and (B) magnetic resonance cholangiopancreatography.

Table 1
Case studies of asymptomatic patients with hyperenzymemia.

Reference	Frequency of patients with normal findings	Frequency of patients with abnormal findings					Image study
		Overall	Cyst	Ductal dilatation or irregularity	Pancreas divisum	Other	
Gullo 1996 ⁴	18/18 (100%)						
Gullo 2000 ⁶	14/19 (74%)					5/19 (26%) were children	
Gullo et al 2009 ¹¹	57/63 (90.5%)	6 (9.5%)	2 (3.2%)	1 (1.6%)	2 (3.2%)	1 (1.6%): anatomic variant of the Wirsung	MRCP
Galassi et al 2014 ⁹	108/207 (88.4%)	15 (7.2%)	2 (0.9%)	6 (2.8%)	6 (2.8%)	1 (0.45%): congenital abnormalities of the Wirsung	

MRCP = magnetic retrograde cholangio-pancreatography.

During this period, all patients received serial measurements of serum amylase, isoamylase, lipase, and image examinations such as abdominal ultrasonography, CT, and/or MRCP. In this study, 183 (88.4%) patients were diagnosed with benign pancreatic hyperenzymemia after excluding salivary hyperamylasemia, and macroamylasemia. Patients in the study group had daily variations and frequent normalizations of serum enzyme levels in tests carried out months or years apart. Among them, 155 patients had an abnormal increase of all three enzymes, 15 patients had an increase in lipase alone, and 13 patients had an increase of only amylase and pancreatic isoamylase, respectively. Moreover, more than half of the patients were found with high (3–7 times above upper normal limit, UNL) or very high (7.1 to 21 times the UNL) levels of lipase. In our current case, the serum lipase level was very high and even reached up to 10 times the level of UNL. In physiologic conditions, lipase secretion into the blood across the basolateral acinar cell membrane is supposed to be faster than other enzymes such as amylase and trypsin.¹¹ This mechanism may explain the different patterns and degrees of hyperenzymemia. Nevertheless, further prospective studies are still needed to validate this result.

The diagnostic yield of “second-level” images such as MRCP and endoscopic ultrasonography in patients with benign pancreatic hyperenzymemia have been evaluated.^{8,10} With the absence of pathological change, the possible cause of pancreatic hyperenzymemia is typically due to a mild obstruction of the pancreatic ductal system, which in turn alters the normal exocytosis process in the acinar cells. MRCP after secretin stimulation could improve visualization of the main pancreatic duct and the duct of Santorini if patients have normal exocrine pancreatic function.¹² The

administration of secretin induces the secretion of fluid and bicarbonate and then increases ductal filling and visualization of the pancreatic tract. However, it is still unclear regarding the association between pancreatic ductal abnormalities and pancreatic hyperenzymemia. The MRCP after secretin stimulation is not available at our hospital and was not performed in this case.

Benign pancreatic hyperenzymemia was previously considered to be a disease afflicting primarily Western populations, and infrequently studied in Asian countries. To the best of our knowledge, these are the first cases of benign pancreatic hyperenzymemia reported in Taiwan. Consequently, physicians should remain aware of this rare, but potentially overlooked disease.

In conclusion, benign pancreatic hyperenzymemia is asymptomatic and generally detected incidentally. It is an uncommon syndrome, particularly in Asian countries. Proper diagnosis is important and can avoid costly duplication of tests, unfounded anxieties, and multiple consultations. However, regular follow-up for these patients is still warranted to exclude pancreatic malignancy.

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