

## Two rare cases of benign hyperlipasemia in children

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### Abstract

Gullo's syndrome is a newly identified condition characterized by a chronic elevation of pancreatic amylase and/or lipase in the absence of pancreatic disease. Until now, only one case of benign isolated hyperlipasemia in children has been recorded. We describe two children with benign and not familial increase of serum lipase. Case 1: a six year old girl presented with occasional discovery of serum lipase elevation. Medical history was silent for pancreatic hyperenzymemia. The screening for possible causes for elevated lipase (genetic, autoimmune and infectious diseases) was normal. The serum lipase increased three fold over the upper limit (193 U/L; reference range 0-60 U/L), with daily fluctuation of values. Both ultrasound scan and magnetic resonance imaging were normal. The genetic mutation associated with chronic pancreatitis was negative. We followed up this patient for two years with blood tests every six months and she did not show any signs or symptoms of pancreatic disease, except for the high level of lipase serum. Case 2: an eight year old girl complained of nausea, vomiting and severe abdominal pain in the

epigastric region after eating for the last two weeks. Full blood count, electrolytes, C-reactive protein, liver and renal function were normal. Serum lipase was 96 U/L (reference range 0-60 U/L). The screening for the possible causes of pancreatic disease was negative. Endoscopy of the upper gastrointestinal tract, ultrasound, computed tomography scan and magnetic resonance imaging were normal. One year after the presentation of the symptoms, the patient became asymptomatic although the level of serum lipase continued to be high.

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**Key words:** Amylase; Lipase; Pancreatic hyperenzymemia; Gullo's syndrome; Benign hyperlipasemia

**Core tip:** Benign hyperlipasemia is a rare condition in children. The identification of this condition could be very useful for pediatricians in the diagnosis and management of hyperlipasemia. The cause of pancreatic hyperenzymemia seems to be related to a defected pathway from the trans-Golgi network to basolateral cell membrane. It has been hypothesized that a defect in this pathway could be responsible for the increased passage of enzymes into circulation. "Gullo's syndrome" remains a diagnosis of exclusion and clinicians still need to be vigilant of the wide-ranging conditions that can manifest initially with elevations in lipase/amylase.

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### INTRODUCTION

Gullo first described in adults a new syndrome character-

ized by a benign chronic increase of serum pancreatic enzymes in the absence of pancreatic or other pathologies<sup>[1]</sup>. This condition is often familial, although sporadic cases have also been described<sup>[2]</sup>. In another study, the same investigator found that this syndrome can also be present in children. In the majority of cases (95%), the hyperenzymemia concerns all pancreatic enzymes; in 5% of cases it is possible to observe an increase of only the amylase and rarely of only the lipase<sup>[3]</sup>. In this report, we describe two pediatric cases of the rare form of benign hyperlipasemia.

## CASE REPORT

### Case 1

A six year old girl came to our outpatient department for the occasional discovery of serum lipase elevation with normal amylase level during routine blood tests. She was third born by normal delivery of non-consanguineous parents. Her medical history was silent except for a surgery because of funicular hernia when she was one year old. There was no familial history of pancreatic hyperenzymemia or of other relevant diseases. At physical exam, her weight, height and body mass index were 20.8 kg, 123.5 cm and 14 kg/m<sup>2</sup> (10<sup>th</sup> centile), respectively; there was no clinical sign of pancreatic or other diseases. Routine blood tests were normal (full blood count, serum glucose, liver and renal function tests, total and fractionated blood bilirubin, blood iron subset and immunoglobulin). In order to assess a possible cause for the elevated lipase level, the following tests were done: lipid subset, cytomegalovirus serology and cultures, Epstein-Barr, toxoplasma, rubella, parvo and herpes virus serology, autoimmunity profile, including anti-transglutaminase antibodies, perinuclear antibodies, antineutrophil cytoplasm and anti-Saccharomyces cerevisiae antibodies, C-peptide and islet cell antibodies, fecal elastase, serum trypsinogen, IgG4 and sweat analysis; they all were within the normal range. Amylase and pancreatic isoamylase as well as serum lipase concentrations were determined by an enzymatic colorimetric method (Beckman Instruments, Fullerton, CA) and the only abnormal parameter was the serum lipase, increased three fold over the upper limit (193 U/L, reference range: 0-60 U/L), with daily fluctuating values. Due to the persistence of increased lipase, abdominal ultrasound scan and magnetic resonance imaging were also performed and did not show any pathological signs. The genetic mutations associated with chronic pancreatitis, including mutations for autosomal recessive cystic fibrosis transmembrane conductance regulator (CFTR) [by two validated commercial kits (INNO-LiPA CFTR 19 and INNOLiPA CFTR 17 Tn polymorphism, Innogenetics N.V., Ghent, Belgium), which simultaneously detect 36 mutations and the Tn polymorphism], autosomal dominant PRSS1 and pancreatic trypsin SPINK1, were also negative, such as the familial screening for pancreatic hyperenzymemia. Having ruled out all the common causes of hyperlipasemia, we decided to follow up this patient with blood tests every six months. For the entire 2 years

of follow up, the child did not show signs or symptoms of pancreatic or other diseases, and blood tests as well as the ultrasound morphology of her pancreas continued to be normal, except for blood lipase levels that fluctuated widely during the whole period of follow up [lipase median value: 194 U/L (reference range: 0-60 U/L) (range: 179-218 U/L); mean  $\pm$  SD: 195.8  $\pm$  12.9 U/L. Pancreatic isoamylase median value: 34.5 U/L (reference range) (0-46 U/L) (range: 30-43 U/L); mean  $\pm$  SD: 35.2  $\pm$  4.5 U/L].

### Case 2

An eight year old girl was referred to our outpatient clinic for abdominal pain for the last two weeks. She complained of nausea, vomiting and severe abdominal pain of short duration localized at the epigastric region, occurring mainly after eating; there was no history of abdominal trauma. On medical examination, she was afebrile, the abdomen was slightly distended and tender; her weight, height and body mass index were 25 kg, 130 cm and 14.8 (25<sup>th</sup> centile), respectively. No weight loss preceded the onset of pain. To exclude organic causes, the following investigations were performed and were normal: full blood count, liver and renal function tests, serum glucose and electrolytes, total cholesterol and fractions, erythrocyte sedimentation rate and C-reactive protein. Serum amylase and lipase concentrations were 124 U/L (reference range 0-46 U/L) and 96 U/L (reference range 0-60 U/L), respectively. Salivary isoamylase and urinary amylase were normal. Amylase became normal in the following five days, while lipase concentrations remained elevated (4-5 fold above the reference value). The diagnostic work-up for pancreatic diseases was started and all the following tests returned within normal range: serology for infective diseases, autoimmunity, fecal elastase, serum trypsinogen, IgG4, sweat test and genetic markers for chronic pancreatitis. Endoscopy of the upper gastrointestinal tract with antral and duodenal biopsies did show any alteration to the esophagus, stomach and duodenal bulb. Morphological assessment (ultrasound scan and magnetic resonance imaging) showed normal pancreatic parenchyma and biliary and pancreatic tree. Familial screening for pancreatic hyperenzymemia was also negative.

During hospitalization, the child recovered from the abdominal pain in the following two days; however, the serum level of lipase remained elevated although it fluctuated. One year after presentation, the patient became asymptomatic although the serum lipase remained elevated [lipase median value: 240 U/L (reference range: 0-60 U/L) (range: 96-480 U/L); mean  $\pm$  SD: 264  $\pm$  166.6 U/L. Pancreatic isoamylase median value: 41.5 U/L (reference range 0-46 U/L) (range: 37-124); mean  $\pm$  SD: 264  $\pm$  166.6 U/L].

## DISCUSSION

Pancreatic hyperenzymemia is a rare finding in children; it can be due to different pathological conditions, the most frequent being acute or chronic pancreatitis<sup>[4,5]</sup>. Other causes of serum lipase elevation have been identified in a

**Table 1 Principal causes for increased serum levels of pancreatic enzymes**

Causes	Suggested work-up
Pancreatic diseases	Full blood count, erythrocyte sedimentation rate, PCR, immunoglobulin
Drugs	Liver function tests
Infections	Fecal elastase
Tumors	Serum trypsinogen
Autoimmunity	IgG4
Trauma	Cytomegalovirus serology and cultures, Epstein-Barr, toxoplasma, rubella, parvo and herpes virus serology
Anatomic anomalies	Sweat analysis
Gene mutation	Genetic analysis (CFTR, PRSS1, SPINK1)
Cystic fibrosis	US
Viral hepatitis	CT scan
Surgery	
Biliary diseases	Full blood count, erythrocyte sedimentation rate, PCR, immunoglobulin
Biliary lithiasis	US scan
Anatomic anomalies	Cholangio-pancreatographic MRI
Tumors	
Sphincter Oddi dysfunction	
Macroenzymemia	Full blood count, erythrocyte sedimentation rate, PCR, immunoglobulin
Celiac disease	Liver function tests
Inflammatory bowel disease	Autoimmune profile: anti-transglutaminase, perinuclear, antineutrophil cytoplasm and anti-Saccharomyces cerevisiae, and islet cell antibodies.
Autoimmune diseases	US scan
Liver diseases	
Lymphoma	
Thyroid cancer	
Renal diseases	Full blood count, erythrocyte sedimentation rate, PCR, immunoglobulin
Inflammatory	Renal function tests
Neoplastic	US scan
Impaired renal function	
Others	Full blood count, erythrocyte sedimentation rate, PCR, serum glucose
Peptic ulcer	Serum cholesterol and triglycerides
Paravaterian diverticulum	US scan
Intestinal obstruction	EGDS
Dyslipidemia	
Diabetic ketoacidosis	
Malignancy	

US: Ultrasound; CT: Computed tomography; CFTR: Cystic fibrosis transmembrane conductance regulator; MRI: Magnetic resonance imaging; EGDS: Esophagogastroduodenal endoscopy; PCR: Polymerase chain reaction.

number of conditions, such as acute cholecystitis, Gilbert syndrome, hypertriglyceridemia, intestinal infarction, duodenal ulcer, obstruction or inflammatory bowel disorders, liver diseases, abdominal trauma<sup>[6]</sup>, diabetes ketoacidosis<sup>[7]</sup> and renal insufficiency (Table 1)<sup>[8]</sup>.

Interestingly, Gullo *et al*<sup>[2]</sup> have recently shown the existence of a benign pancreatic hyperenzymemia defined as an abnormal increase in serum pancreatic enzymes that occurs in healthy adults or children in the absence of pancreatic or other disease; it is asymptomatic and persists over time with considerable fluctuation in serum enzyme concentrations. At least 1-2 years must pass after the initial finding of the hyperenzymemia before it can be considered benign. It can be familial (when the patient has at least one family member with the same anomaly) or sporadic. The authors studied this condition in 15 children with hyperenzymemia. Among them, 13 were found with high levels of all pancreatic enzymes, one with normal range of enzymes, and only one was found with an increased level of the only lipase. The condition was familial in 12 children and sporadic in three of them. To our knowledge, there are no other studies in children re-

porting the isolate benign increase of serum lipase, while two studies recorded one case each of familial hyperamylasemia<sup>[9,10]</sup>.

In this report, we described the second two cases in the literature of benign hyperlipasemia. During the whole period of follow-up, the two children did not present with any signs or symptoms of pancreatic or other diseases, and blood tests as well as the ultrasound morphology and the imaging study of their pancreas remained normal, showing the benign nature of this abnormality. A limitation of the present case report may be the non-availability of the nasal potential difference test for the diagnosis of subclinical form of cystic fibrosis, although genetic screening and sweat analysis were negative. In the second case, initial elevations of both amylase and lipase with ongoing persistence in lipase may suggest a pancreatic origin, but not detectable based on limitations of current available tests. It is important to point out that, even if rarely (1%-2% of cases), an apparently benign pancreatic hyperenzymemia can be the first clinical sign of a pancreatic tumor, which may declare itself in the following years<sup>[2]</sup>.

In our experience, these cases were sporadic, considering that familial enzymes were normal. The cause of pancreatic hyperenzymemia and the reason for its fluctuating behavior is not known. It has been shown that there is a direct, constitutive-like pathway from the trans-Golgi network to the basolateral cell membrane, by which newly synthesized enzymes reach the circulation. It has been hypothesized that a defect in this pathway could be responsible for the increased passage of enzymes into circulation<sup>[2]</sup>.

The fluctuating behavior could depend on the degree of the cellular defect, with the passage of enzymes being sporadic when the defect is mild and more frequent when it is more severe or extensive<sup>[2]</sup>.

“Gullo’s syndrome” remains a diagnosis of exclusion and clinicians still need to be vigilant of the wide-ranging conditions that can manifest initially with elevations in lipase/amylase. However, clinicians should be aware that failing to diagnose the cause, the condition of idiopathic hyperlipasemia (or hyperamylasemia) can be diagnosed and is usually associated with a benign course. According to Gullo, we believe that the knowledge of this condition should be helpful to the pediatrician in diagnosis and management, assuring the clinician and alleviating the concern of the child’s parents<sup>[1]</sup>. A larger cohort of patients and longer follow-up are needed to evaluate the exact proportion of this clinical chemical constellation and to better understand the etiology, natural history and the real benign nature of this condition.

## COMMENTS

### Case characteristics

The two cases of benign hyperlipasemia have a different clinical presentation; while the first case was asymptomatic, the second case showed nausea, vomiting and severe abdominal pain at the epigastric region.

### Clinical diagnosis

Medical examination was silent for pancreatic diseases.

### Laboratory diagnosis

The screening for possible causes for elevated lipase and amylase (genetic, autoimmune and infectious diseases) was normal.

### Pathological diagnosis

In the second case, endoscopy of the upper gastrointestinal tract with antral

and duodenal biopsies did show any alteration to the esophagus, stomach and duodenal bulb.

### Related reports

It is very important to know this condition because an apparently benign pancreatic hyperenzymemia can be the first clinical sign of a different pathological condition.

### Experiences and lessons

Benign hyperlipasemia remains a diagnosis of exclusion and clinicians still need to be vigilant of the wide-ranging conditions that can manifest initially with elevations in lipase/amylase.

### Peer review

This report describes the second two cases in the literature of benign hyperlipasemia but a larger cohort and longer follow-up are needed to better understand the natural history of this condition.

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