

# Benign pancreatic hyperenzymemia or Gullo's syndrome

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## ABSTRACT

Benign pancreatic hyperenzymemia is a newly identified syndrome characterized by an abnormal increase in serum pancreatic enzymes in the absence of pancreatic disease. The hyperenzymemia can occur sporadically or in a familial form, and all of the pancreatic enzymes show elevations. Although the condition is persistent, the enzyme elevations fluctuate considerably, even temporarily returning to normal levels at times. In this review the main characteristics of this syndrome are described.

**Key words:** pancreatic enzymes, pancreatic diseases, pancreatic imaging, Gullo's syndrome

## INTRODUCTION

An increase in serum levels of pancreatic enzymes is a well known manifestation of pancreatic disease, especially acute pancreatitis. In 1996 one of us (L.G.) described a new syndrome characterized by a chronic, benign, abnormal increase in concentrations of serum pancreatic enzymes including amylase, pancreatic isoamylase, lipase and trypsin [1]. These enzymes were studied in 18 healthy subjects who had been sent to the author after elevated serum pancreatic enzyme levels raised the suspicion of pancreatic disease. In most of these subjects the hyperenzymemia was discovered incidentally when tests for pancreatic enzymes were carried out as a part of a routine work-up, with no specific indication. All of the subjects were in an optimal state of health, with no clinical evidence of illness; in addition, all of their routine blood test results were normal, as were imaging studies of the pancreas. The pancreatic enzyme elevations were most often in the range of 2 to 4 times normal but were sometimes much higher, up to 15 times normal in one of the 18 subjects. I would like to point out that this study was lengthy: it involved subjects referred to the author from January 1987 to June 1991, all of whom were followed until December 1995, i.e., until shortly before publication of the study [1]. In addition, since formal conclusion of the study in 1995 follow-up of most of these subjects was continued until now (December 2007). It has been ascertained that the hyperenzymemia has persisted as has the absence of pancreatic disease; thus, the benign nature of this condition has been clearly demonstrated.

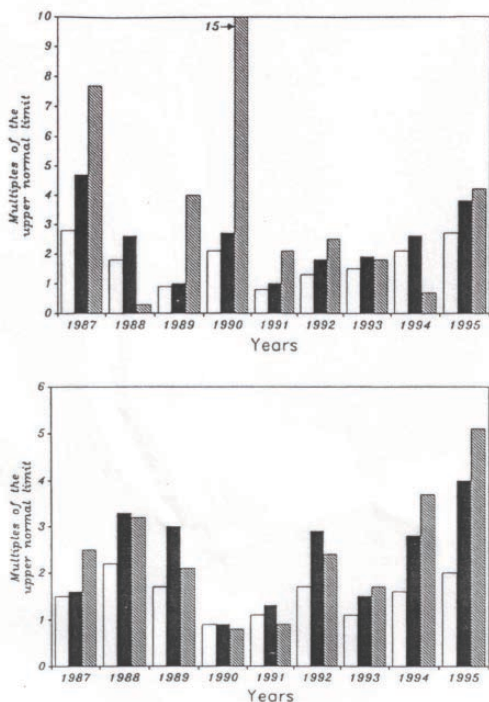
## REVIEW

Since this initial description the same author (L.G.) has continued to see other subjects with benign pancreatic hyperenzymemia (BPH), among whom there have also been familial cases, including children. In a study published in 2000 [2] he described seven families in each of which two or more members had this anomaly, for a total of 19 subjects, five of whom were children under 10 years of age. Benign pancreatic hyperenzymemia in children was also described, in detail, in a recent study of 15 children with this condition [3]. In these children the hyperenzymemia was discovered incidentally or after adult subjects known to have the hyperenzymemia were asked to have their children tested for it.

In another study [4] done with the scope of determining the effect of secretin administration on serum levels of pancreatic enzymes in 20 subjects with this form of hyperenzymemia, it was found that this hormone, which normally weakly stimulates the passage of pancreatic enzymes into circulation, caused a significant serum increase in these subjects, particularly of lipase. Thus it appears that the exuberant passage of pancreatic enzymes into the blood occurs in response to hormonal stimulation as well as in basal conditions.

In previous studies [1,2] it was shown that subjects with benign pancreatic hyperenzymemia show wide variations in serum pancreatic enzyme concentrations and even normalizations in tests carried out months or years apart (*Fig. 1*). Recently a study to determine whether significant

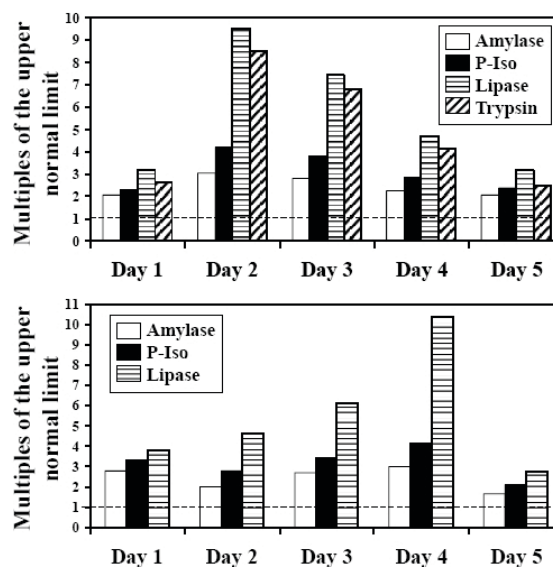
**Figure 1.** Sequential measurements of serum amylase (□), pancreatic isoamylase (◻), and lipase (▨) concentrations in 2 study subjects. Values are shown as multiples of the upper normal limit. (Reprinted from: Gulló L. Chronic nonpathological hyperamylasemia of pancreatic origin. *Gastroenterology*. 1996 Jun;110(6):1905-8, with permission from American Gastroenterological Association).



variations occur on a day-to-day basis was undertaken [5]. To this end, serum concentrations of pancreatic enzymes were determined for five consecutive days in 42 subjects with benign pancreatic hyperenzymemia. It has been shown that the enzyme concentrations remained elevated, albeit with wide fluctuations, for all five days of the study in only eight (19%) of the 42 subjects studied (*Fig. 2*). In the great majority ( $n=33$ ; 78.6%) the enzyme concentrations not only varied considerably from one day to the next, but also normalized. The number of normalizations that occurred varied from one to four out of five determinations (*Fig. 3*). This rapid see-sawing of serum enzyme levels from one day to the next was a surprising finding, one that has never been reported until now. In most of the subjects studied, 37 of the 42, all of the enzymes were abnormally high, with lipase and trypsin generally showing the greatest increases, from 3 to 7 times normal values in the majority of cases. In 3 of the 42 only amylase was elevated, in one only lipase, and in the remaining subject all of the enzyme levels were normal. In this last subject enzyme elevations were seen at several determinations performed prior to and after this study.

The reason for the pancreatic hyperenzymemia and for its fluctuating behavior is not known. In a paper on the intracellular transport of pancreatic enzymes, Cook et al. [6] showed that there is a direct, constitutive-like pathway from

**Figure 2.** Serum amylase, pancreatic isoamylase (P-Iso), and lipase concentrations during 5 consecutive days in 2 subjects. Trypsin concentrations are also seen in 1 of the 2. Enzymes are abnormally elevated, albeit with wide fluctuations, for all 5 days of the study. Values are shown as multiples of the upper normal limit (broken line). (Reprinted from: Gulló L. Day-to-day variations of serum pancreatic enzymes in benign pancreatic hyperenzymemia. *Clin Gastroenterol Hepatol*. 2007 Jan;5(1):70-4, with permission from American Gastroenterological Association).

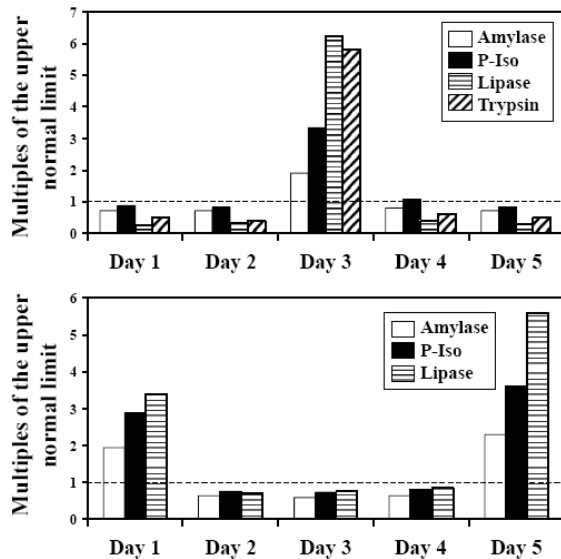


the trans-Golgi network to the basolateral cell membrane by which newly synthesized enzymes reach the circulation. A defect in this pathway could be responsible for the increased passage of enzymes into circulation. The fluctuating pattern of enzyme release could depend upon the extent of the cellular defect, with the passage of enzymes being sporadic when the defect is mild, more frequent when it is more severe. The size of the increments could also be related to the extent of the defect. This hypothesis is supported by the fact that the subjects who had abnormal elevation for all five days of the study also had the highest degrees of elevation [5].

In another study [7] we evaluated whether mutations of the gene for cystic fibrosis could have an etiological role in this form of pancreatic hyperenzymemia. We studied 70 subjects with the hyperenzymemia and found that the frequency of these mutations was similar to that found in the general population, thus excluding an etiological role for this gene. In these same subjects we also calculated the frequency of SPINK1 and PRSS1 gene mutations; again, there was no significant difference with respect to the general population [8].

In our last published study [9], we showed that BPH may be found in family members of patients with pancreatic cancer. The significance of this association is not clear, but the possibility that these individuals could be at increased risk of pancreatic cancer cannot be excluded.

**Figure 3.** Serum amylase, pancreatic isoamylase (P-Iso) and lipase concentrations during 5 consecutive days in 2 other subjects. Trypsin concentrations are also seen in 1 of the 2. Enzymes are abnormally elevated for only 1 day in 1 subject and for 2 days in the other. Values are shown as multiples of the upper normal limit (broken line). (Reprinted from: Gullo L. Day-to-day variations of serum pancreatic enzymes in benign pancreatic hyperenzymemia. *Clin Gastroenterol Hepatol.* 2007 Jan;5(1):70-4, with permission from American Gastroenterological Association).



Other than the above-mentioned studies, very little has been written about this condition. In a letter to the editor that appeared after publication of the first article [1] on this syndrome, Cavallini et al. [10] reported a group of 30 healthy subjects who had pancreatic hyperenzymemia, 13 of whom also had hypercholesterolemia and/or hypertriglyceridemia. These authors postulated that the abnormal increase of serum pancreatic enzymes in their study group was caused by pancreatic steatosis that, in turn, was due to the dyslipidemia. The diagnosis of pancreatic steatosis was made by these investigators on the basis of the ultrasonographic finding of a hyperechogenic pancreas. This conclusion is, however, untenable for two reasons: first of all because there is no proof that pancreatic steatosis actually exists in humans; and, secondly, because the belief that ultrasonographic hyperechogenicity of the pancreas indicates with certainty the presence of fat in this organ has been largely abandoned [11]. In addition, we have recently published a study [12] in which we used magnetic resonance imaging to determine whether the pancreas of 18 healthy subjects with dyslipidemia and with benign pancreatic hyperenzymemia is a fatty pancreas, but we found no signs of fatty infiltration of the pancreas in any of the subjects studied.

In another letter to the editor written after to that first article [1], a group of Spanish authors [13] reported 5 cases of sporadic pancreatic hyperenzymemia, concluding that their cases were similar to those described in the published article. Some of the subjects with benign pancreatic hyperenzymemia

that we have been following have also been found to have Gilbert's syndrome [14], an apparently benign increase in creatine phosphokinase or Rowland's syndrome [15], or increased transaminases in the absence of hepatic disease [16]. It is not known if these conditions are in some way connected or if their association is coincidental.

We recently saw a healthy young woman who had pancreas divisum and pancreatic hyperenzymemia, an association that has also been reported by other authors [17]. In this case as well we do not know if the association is coincidental or whether there is a causal relationship.

In another case, an apparently healthy 56-year-old man was referred to us eight years ago for pancreatic hyperenzymemia. He had no signs or symptoms of pancreatic disease and clinical examination, abdominal ultrasound and computerized tomography were all negative. Unfortunately, he returned a year later when he developed jaundice, at which point imaging studies revealed the presence of pancreatic cancer. The question that arises is whether the initial enzyme elevations were an early manifestation of pancreatic cancer, or did this patient have benign pancreatic hyperenzymemia on which pancreatic cancer was later superimposed? From a practical standpoint, this case teaches us that all subjects with an apparently benign pancreatic hyperenzymemia who are over 50 years of age should be followed for 1-2 years before the hyperenzymemia is designated as benign.

As far as the diagnosis is concerned, in addition to clinical history and physical examination, routine blood analysis including liver and renal function tests, abdominal ultrasonography and computed tomography are generally sufficient to exclude pancreatic diseases. I often perform magnetic resonance imaging mainly to examine the Wirsung duct and to exclude the presence of small intraductal tumors, or other underlying pancreatic disease. Endoscopic ultrasonography may be performed in particular cases, mainly when the previously mentioned imaging studies are negative but a clinical suspicion of early tumor remains [18,19].

It is important to note that the diagnosis of benign pancreatic hyperenzymemia should not be made until a period of observation of at least 1 year has passed, during which there are no symptoms or signs of pancreatic disease and pancreatic structure remains normal. Another simple and useful diagnostic criterion is the day-to-day fluctuations in enzyme values from high to low or vice versa that can occur with the benign syndrome.

In the past several works have been written on the benign elevation of amylase alone, and the principal explanations offered for this finding have been that this hyperamylasemia could be due to the presence of macroamylase in circulation, an increase in salivary amylase, or the presence of an amylase that may be neither pancreatic nor pathological [20-24]. The existence of a salivary and pancreatic or only pancreatic hyperamylasemia as been very rarely reported [20-24].

## CONCLUSIONS

1. Benign pancreatic hyperenzymemia is a new syndrome characterized by serum pancreatic enzyme elevations in the absence of pancreatic disease; it occurs in either sporadic or familial form. It is asymptomatic and is generally discovered incidentally.
2. The hyperenzymemia is present both in basal conditions and after pancreatic stimulation with secretin. It persists over time with considerable fluctuation in serum enzyme concentrations, including frequent normalizations, that can occur on a day-to-day basis. In about 90-95% of the cases, serum levels of all of the pancreatic enzymes are elevated; in the remaining 5-10% only amylase or, more rarely, only lipase levels are increased. The enzyme elevations vary considerably from one subject to another and from day to day in the same subject; generally, the increase is in the range of 1.5-2 to 6-7 times normal values, with lipase and trypsin generally being more elevated than amylase. In some cases, the serum enzymes increase more than 10 times normal.
3. CFTR, SPINK1 and PRSS1 gene mutations do not seem to have a role in the etiology of the hyperenzymemia.
4. At least 1 year must pass after the initial finding of pancreatic hyperenzymemia before it can be considered benign. It is important to remember that, even if rarely (1-2% of cases), an apparently benign pancreatic hyperenzymemia can be the first clinical sign of a pancreatic tumor.
5. Proper diagnosis of this form of hyperenzymemia is important because it reassures the subject having this anomaly that the syndrome is benign and that he does not have pancreatic disease, and because it can prevent multiple and complex diagnostic tests or hospital admissions. This is important especially for children.

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