

## EDITORIAL

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# Chronic Asymptomatic Pancreatic Hyperenzymemia: Is It a Benign Anomaly or a Disease?

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High concentrations of serum pancreatic enzymes in asymptomatic subjects are not just an occasional laboratory finding but are of clinical interest as they raise questions about whether or not to conduct investigational procedures and what kinds. Frequently, these questions come from general practitioners and include assays for amylase and/or (though less frequently) lipase in routine blood tests. The main question is whether asymptomatic pancreatic hyperenzymemia should be considered a benign syndrome without clinical significance or a biochemical sign of a subclinical disease including, in particular, pancreatic disease.

Gullo is the author who, better than anyone, studied the clinical implications of pancreatic hyperenzymemia in asymptomatic subjects. In 1996, he described, for the first time, in asymptomatic adults, a syndrome involving persistent abnormal increases in serum amylase, pancreatic isoamylase, lipase and trypsin, with no evidence of pancreatic disease by imaging [1]. He initially called this picture “chronic non-pathological pancreatic hyperenzymemia (CNPH)” (1996), then, later “benign pancreatic hyperenzymemia” or “Gullo’s syndrome” [2, 3, 4]. He noted that the syndrome occurred sporadically or in a familial form [5], and that usually serum levels of both amylase and lipase presented wide fluctuations, with occasional transient normalization in some cases [1]. The extent of the increase ranges from 1.1 to 10 times the upper normal limit for pancreatic amylases, and from 1.1 to

16 times for lipase but most often from 2 to 4 times [1, 2, 3, 4, 5, 6].

Gullo and Migliori also reported that this syndrome can be marked by day-to-day fluctuations in serum pancreatic enzymes and that this finding can be used as a simple diagnostic criterion [7]. The syndrome was called “familial pancreatic hyperenzymemia” when a patient with persistent pancreatic hyperenzymemia but no pancreatic disease had at least one family member with the same anomaly [5].

In clinical practice, before deciding that someone has CNPH, it is essential to carefully assess the clinical history and do some other biochemical tests since pancreatic hyperenzymemia, in subjects without abdominal symptoms can be associated with celiac disease, viral hepatitis, dyslipidemia or macroenzymemia, as noted by Frulloni *et al.* in an editorial previously published in this Journal [8]. The determination of serum macroamylase, or 24-hour urinary amylase, as a less expensive alternative is indicated in subjects with hyperamylasemia alone, but not in those with hyperlipasemia because it is almost always negative. It is also useful to measure serum cholesterol and/or triglycerides because they may be high in some subjects with pancreatic hyperenzymemia.

The existence of an etiological relationship between dyslipidemia and pancreatic hyperenzymemia remains uncertain. Some authors [9] have suggested this causal relationship on the basis of interpreting the hyperechoic pancreas at ultrasonography, detectable in some of these subjects, as an expression of pancreatic fat infiltration and pancreatic steatosis. This was assumed to be the cause of the pancreatic hyperenzymemia in the same way as hepatic steatosis results in high transaminases. However, the existence of pancreatic steatosis is still under debate and the lack of signs of fatty infiltration by magnetic resonance in these subjects does not seem to support this hypothesis [6]. Careful evaluation of the clinical history is important in order to exclude the role of drugs (paracetamol,

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**Abbreviations** CNPH: chronic non-pathological pancreatic hyperenzymemia; s-MRCP: secretin-MRCP

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steroids, azathioprine), a subclinical systemic disease or malignancy, although, in such cases, we are more likely to be seeing a patient and not an apparently healthy, asymptomatic subject.

When increased serum concentrations of pancreatic amylase and/or lipase are confirmed by repeated assays, the question arises as to whether one should follow a "wait and see" strategy, assuming a real but non-pathological biochemical alteration, or proceed with a diagnostic workup, considering it a biochemical sign of a subclinical pancreatic disease.

In Gullo's various case studies, the subjects were defined as having CNPH after the exclusion of pancreatic abnormalities by repeated ultrasonography in almost all cases, computer tomography in some and ERCP in a few. These data explain why ultrasonography alone is usually recommended for evaluation of the pancreas in subjects with CNPH, assuming that additional, more expensive, in some cases invasive, diagnostic procedures are not justified [1].

However, the diagnostic yield of "second-level" imaging, such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS), in subjects with CNPH has been examined in some recent studies [6, 10, 11, 12, 13]. Compared to US and CT, MRCP and/or EUS both depict the pancreatic ductal system better and, in the case of EUS, also the parenchyma. MRCP is the most widely investigated "second-level" imaging procedure in subjects with persistent high levels of serum pancreatic amylases and/or lipases but no clinical signs or symptoms of pancreatic disease. MRCP findings are reported in five studies [6, 10, 11, 12, 13] and summarized in the Table. In 147 out of a total of 224 subjects, MRCP indicated normal ductal findings. The findings were abnormal in 34.6%: ductal dilatation and/or irregularity, pancreas divisum, small cyst/s and others (intraductal papillary mucinous tumors, sphincter of Oddi dysfunction).

In asymptomatic subjects with pancreatic hyperenzymemia, our group found that, under secretin stimulation, MRCP (s-MRCP) boosted the detection of pancreatic ductal abnormalities as compared to MRCP without secretin. s-MRCP showed abnormal ductal and side branch findings consistent with early-stage chronic pancreatitis in about one-third of cases, according to the Cambridge classification of ductal pancreatic morphology [14], more than four times that detected by MRCP alone. The overall frequency of abnormal ductal MRCP findings in asymptomatic subjects with pancreatic hyperenzymemia detected by our group was similar to that observed by Morteale *et al.* [10] and Frulloni *et al.* [13] (>50% of cases in both studies) and higher than that described by Pezzilli *et al.* [12] (18.0%) and Gullo *et al.* [6] (9.5%).

From a pathogenic point of view, the question is whether these pancreatic ductal abnormalities explain the high serum levels of pancreatic enzymes. One can suppose that pancreatic hyperenzymemia is a result of difficulty in discharging pancreatic juice and, as a

consequence, its enzymatic content, through the sphincter of Oddi into the duodenal lumen, as in the case of delayed main pancreatic duct emptying or pancreas divisum. However, the similar frequency of delayed main pancreatic duct emptying shown by s-MRCP in the few subjects with pancreatic hyperenzymemia and patients with upper abdominal pain without pancreatic hyperenzymemia (Testoni *et al.* [11]) seems to exclude a causal relationship between the high enzyme levels and difficulties in draining pancreatic juice out through the sphincter of Oddi.

The study of Morteale *et al.* [10] compared the frequency of pancreas divisum in subjects with pancreatic hyperenzymemia with that found in a large control population consisting of patients undergoing MRCP for a variety of clinical indications. The frequency of pancreas divisum in the study group was significantly higher (18.5%) than in the control group (6.4%) but this obstructive pathogenesis of the enzyme elevation can be questioned because the subjects with this ductal abnormality and pancreatic hyperenzymemia had no morphological evidence of ductal obstruction. This appeared to be confirmed in our study [11] by the normal outflow of pancreatic juice through the minor papilla under secretin stimulation.

This difficulty in attributing the potential obstructive abnormality of pancreatic hyperenzymemia to pancreas divisum recalls its even more debated role in acute recurrent pancreatitis.

Gullo *et al.* reported other considerations sustaining a merely coincidental finding rather than a causal relationship between hyperenzymemia and pancreatic abnormalities [6]: a) the typical fluctuations in enzyme behavior would presumably not occur if the cause was a fixed pancreatic lesion or anomaly nor would there be an increase in only one enzyme, as is observed in some cases; b) the enzyme level changes in the morning after overnight fasting, when pancreatic secretion is not stimulated and is, in fact, minimal or absent; c) the dilatation of secondary pancreatic ducts alone has no clear pathological significance; d) the lack of evidence that an isolated solitary small pancreatic cyst (less than 1 cm) can cause an increase in serum pancreatic enzymes; e) the long-standing increase of pancreatic enzymes, in some cases for more than 20-30 years.

Therefore, all these points prompt a question: if there is no causal relationship between asymptomatic pancreatic hyperenzymemia and pancreatic morphological abnormalities, are the latter merely occasional findings, enough to justify not doing a pancreatic diagnostic evaluation?

To give an answer, it would be important to have controlled data but unfortunately, except for two controlled trials, one retrospective [10] and one prospective [11], only observational studies have been reported apart from the MRCP studies already mentioned. These two trials concluded that there was a significantly higher frequency of pancreas divisum [10] and ductal findings consistent with chronic pancreatitis

[11] in asymptomatic subjects with pancreatic hyperenzymemia than in subjects examined by MRCP for indications other than pancreatic enzymatic elevation [10] or patients with non-pancreatic upper abdominal pain without high enzymes, respectively [11].

In a recent prospective study [12], 75 asymptomatic subjects with long-standing pancreatic hyperenzymemia examined by abdominal US were evaluated, when considered necessary, by second-level imaging procedures, such as abdominal CT and/or MRCP and/or EUS. In total, 88% were examined by more than one procedure: two procedures in 50%, three in 33.3% and four in 16.7% (Pezzilli *et al.*, 2009 [12]). In 37 of these 75 subjects (50.7%), pancreatic or extrapancreatic disease was detected: chronic pancreatitis (26.7%), autoimmune chronic pancreatitis (1.3%), benign pancreatic cyst (1.3%), serous cystadenoma (2.7%), intraductal papillary mucinous tumor (6.7%), ductal pancreatic adenocarcinoma (4.0%). Of the remaining 38 subjects, 4.0% had macroamylasemia, 4.0% familial hyperenzymemia and 41.3% CPNH. The authors concluded that some pancreatic and/or extrapancreatic disease can be detected in about half the subjects with CPNH by second-level imaging.

Patients with abnormalities consistent with the diagnosis of chronic pancreatitis merit particular comment. In the studies listed in the Table, chronic pancreatitis was diagnosed by MRCP according to the Cambridge classification of ductal pancreatic morphology, except in the study that used EUS [12] where the diagnostic criteria were not reported.

The criteria for diagnosing chronic pancreatitis have often been debated in an attempt to achieve a consensus. EUS is considered the reference procedure, but the diagnosis is considered to be most reliable only when more than four (Wiersema *et al.*) [15] or at least two established major or one major and two minor (Catalano *et al.*) [16] ductal and/or parenchymal EUS criteria are present. In our experience, very few asymptomatic subjects with pancreatic hyperenzymemia fulfill these criteria (personal data). Although these diagnostic considerations are important, further prospective and controlled trials are needed to clarify whether pancreatic morphological abnormalities in asymptomatic subjects with high pancreatic enzymes are more frequent than in controls.

While awaiting further controlled trials, I think that the detection of pancreatic abnormalities in about one-third to one-half of asymptomatic subjects with pancreatic hyperenzymemia should indicate the necessity of the following diagnostic work-up: once non-pancreatic hyperamylasemia is excluded (normal level of salivary isoamylase and urinary amylase or absence of macroamylase) and, considering the low sensitivity of pancreatic ultrasonography for detecting small pancreatic lesions even in the hands of an experienced examiner, any person with either pancreatic hyperamylasemia or lipasemia, especially people with recently confirmed high enzyme levels, should be sent to referral centers and examined by contrast-enhanced MR with MRCP, ideally with secretin stimulation, or EUS, to assess both the parenchymal and pancreatic ductal system. The choice of the procedure depends on the availability and expertise of the examiners.

In subjects with no evidence of pancreatic disease after this first diagnostic approach, an imaging follow-up in which at least one of the above procedures is repeated should be considered after about a year, before the hyperenzymemia can be defined with certainty as non-pathological or benign.

**Conflict of interest** The authors have no potential conflicts of interest

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**Table.** MRCP findings in studies on asymptomatic subjects with pancreatic hyperenzymemia.

	No. of subjects	Frequencies of subjects with normal findings	Frequencies of subjects with abnormal findings				Controls	
			Overall	Small cyst(s)	Ductal dilatation and/or irregularity	Pancreas divisum		Others
Mortele <i>et al.</i> , 2004 [10]	54	23 (42.6%)	31 (57.4%)	7 (13.0%)	9 (16.7%)	10 (18.5%)	5 (9.3%)	Yes
Frulloni <i>et al.</i> , 2007 [13]	32	14 (43.8%)	18 (56.3%)	0 (0%)	10 (31.3%)	5 (15.6%)	3 (9.4%)	No
Gullo <i>et al.</i> , 2009 [6]	63	57 (90.5%)	6 (9.5%)	2 (3.2%)	1 (1.6%)	2 (3.2%)	1 (1.6%)	No
Testoni <i>et al.</i> , 2009 [11] <sup>a</sup>	25	12 (48.0%)	13 (52.0%)	1 (4.0%)	8 (32.0%)	2 (8.0%)	3 (12.0%)	Yes
Pezzilli <i>et al.</i> , 2009 [12]	50	41 (82.0%)	9 (18.0%)	6 (12.0%)	2 (4.0%)	0 (0%)	1 (2.0%)	No
<b>Total</b>	<b>224</b>	<b>147 (65.6%)</b>	<b>77 (34.6%)</b>	<b>16 (7.1%)</b>	<b>30 (13.4%)</b>	<b>19 (8.5%)</b>	<b>13 (5.8%)</b>	-

<sup>a</sup> secretin-MRCP

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