Endoscopic Ultrasonography May Select Subjects Having Asymptomatic Chronic Pancreatic Hyperenzymemia Who Require a Stricter Follow-up

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Objectives: We have previously shown that at least 50% of patients with asymptomatic chronic pancreatic hyperenzymemia (ACPH) may develop morphological pancreatic alterations. Endoscopic ultrasonography (EUS) may detect small lesions, and its sensitivity seems to be higher than other imaging techniques. The aim of this study was to evaluate whether EUS may modify the management of patients having ACPH.

Methods: In 2 referral centers for pancreatic disease, a retrospective analysis of prospectively enrolled patients with ACPH was conducted.

Results: Seventy-three patients with ACPH were enrolled for the purpose of this study. Endoscopic ultrasonography was performed as the last examination in 45 subjects who resulted negative at previous imaging studies (abdominal ultrasound, computed tomography, magnetic resonance imaging associated with cholangiopancreatography). Using EUS in 7 subjects, abnormalities were found in the following: 3 branch-duct intraductal papillary mucinous neoplasms, 1 duodenal diverticulum, 1 annular pancreas, 1 findings suggestive of chronic pancreatitis, and 1 undefined cyst (<5 mm).

Conclusions: Endoscopic ultrasonography is able to detect alteration not found by other imaging technique in 15.5% of patients with ACPH and may be useful to select those patients who require a more strict follow-up.

Key Words: pancreas, pancreatic hyperenzymemia, pancreatic cyst, EUS, chronic pancreatitis, hyperamylasemia

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Asymptomatic chronic pancreatic hyperenzymemia (ACPH) is defined as a chronic, abnormal increase in the serum concentrations of the pancreatic enzymes, including amylase, pancreatic isoamylase, lipase, and trypsin, without abdominal pain of pancreatic origin and morphological alterations of the pancreatic gland at imaging techniques.[1,2] It occurs in either sporadic or familial form[3] and can persist over time with wide variations in serum enzyme concentrations, with possible temporary normalization.[2] Enzyme elevations are most often related both to amylase and lipase, in the range of 2 to 4 times normal (but can sometimes be much higher), with lipase often being more elevated than amylase. In rare occasions, only amylase or lipase is abnormal.[2,4] Nowadays, the definition of ACPH should be reserved to those asymptomatic patients without previous diagnosis of pancreatic disease and without (*a*) a condition potentially causing pancreatic hyperenzymemia (alcohol abuse, previous digestive surgery) and (*b*) a nonpancreatic cause of hyperamylasemia/hyperlipasemia (salivary hyperamylasemia, renal disease, viral hepatitis, celiac disease, dyslipidemia, drugs, macroamylasemia or macrolipasemia, lung and ovarian cancer).[5,6]

However, in recent years, studies conducted with high-resolution imaging techniques have revealed pancreatic abnormalities in a significant proportion of patients initially diagnosed as having ACPH,[7–10] and one of us (R.P.) has shown that at least 50% of patients with ACPH may develop morphological pancreatic alterations on follow-up.[6] These new findings can be explained by the development and widespread use of more advanced second-level imaging procedures for the evaluation of biliary and pancreatic disease, which allows detection of small pancreatic lesions with a sensitivity higher than older imaging techniques. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) are considered the most accurate imaging methods for evaluating the pancreas and ductal system.[11,12] However, although MRCP is the most widely investigated second-level imaging examination in subjects with ACPH, the role of EUS in those patients is not well defined.

The aim of this study is to evaluate the possible presence of pancreaticobiliary alterations using EUS in subjects with ACPH whom previous evaluation with other imaging techniques did not result in a specific diagnosis. The ancillary aim was to assess whether the results of EUS may modify the management of those patients.

MATERIAL AND METHODS

Patients and EUS Examination

All patients with ACPH identified from January to December 2013 from prospective databases at 2 referral centers in Italy (Sant'Orsola-Malpighi Hospital, Bologna; A. Murri Hospital, Fermo) were enrolled in the study. Asymptomatic chronic pancreatic hyperenzymemia was defined as an increase of serum amylase and/or lipase above the upper normal limits for more than 6 months, in asymptomatic subjects older than 18 years, without previous diagnosis of pancreatic disease. Exclusion criteria included the following: salivary hyperamylasemia, renal insufficiency, viral hepatitis, celiac disease, dyslipidemia, biliary stones, macroamylasemia and/or macrolipasemia, lung and ovarian cancer, alcohol abuse (≥40 g/d), and previous digestive surgery. Subject with ACPH with at least 1 member of the family having the same serum enzyme alteration was diagnosed as having familial hyperenzymemia.[3,6]

All EUS procedures were performed as the last examination considered necessary on the basis of the physician's evaluation in subjects who had negative results in previous imaging studies (abdominal ultrasound (US), computed tomography (CT), MRCP). Endoscopic ultrasonography was performed with the patient

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under conscious sedation by experienced endoscopists (F.A. and N.P.) using a radial (GF-UE160-AL5; Olympus, Hamburg, Germany) or linear (GF-UCT140-AL5; Olympus) echoendoscope. Pancreatic changes suggestive of chronic pancreatitis were assessed using the Rosemont criteria.[13]

Ethics

The study was approved by the senior staff committee of the Department of Digestive Diseases and Internal Medicine of the University of Bologna and that of ASUR Marche and was carried out in accordance with the Helsinki Declaration of the World Medical Association.

All patients provided written consent for the procedures performed, and all examinations were those usually performed to evaluate the presence of pancreatic diseases.

Statistics

Data are reported as mean values, standard deviation (SD), range, and frequencies. The Mann-Whitney *U* test and the χ^2 test were used where appropriate. Data were managed with the SPSS statistical package (Version 13.0; SPSS Inc, Chicago, Ill). A 2-tailed *P* value of less than 0.05 has been considered significant.

RESULTS

Altogether, 73 consecutive patients were enrolled in the 2 centers for the purpose of this study (35 males; 38 females; mean age, 58.9 years; range, 22–91 years). The mean (SD) duration of pancreatic hyperenzymemia was 8.7 (4.6) years. Mean amylase concentration was 304 IU/L (range, 101–2082; upper normal limit, 110 IU/L) and mean lipase concentration was 248 IU/L (range, 25–2941; upper normal limit, 60 IU/L) (Table 1). In 11 (15%) of the 73 subjects, the abnormally elevated serum enzyme levels showed temporary normalization (7 subjects with hyperamylasemia, 3 with hyperlipasemia, and 1 with hyperamylasemia and hyperlipasemia). Seven subjects had a familial ACPH, and their amylase and lipase concentrations were not statistically different as compared with those of 66 patients having sporadic ACPH ($P = 0.790$). Sixty-one patients (83.5%) underwent US, CT was carried out in 32 patients (43.8%), 41 subjects (56.1%) underwent MR imaging associated with MRCP, and 1 patient (1.3%) was subject to ERCP. All these imaging studies did not reveal morphological alterations of the pancreaticobiliary tract.

In 45 patients (61.6%), a EUS was also performed and using this technique, pancreatic or biliary system abnormalities were found in the following 7 subjects (Table 2): 3 branch duct intraductal papillary mucinous neoplasms (IPMNs) (BD-IPMNs), 1 duodenal diverticulum, 1 annular pancreas, 1 undefined pancreatic cyst, and 1 EUS finding suggestive of chronic pancreatitis, according to the Rosemont criteria. The 3 BD-IPMNs detected with EUS are greater than 12 mm, and 2 of them have been unrevealed by previous US and MRCP. The small pancreatic cyst (4.4 mm) remained undefined because of the impossibility to establish a clear communication with the main pancreatic duct although. The mean (SD) duration of ACPH in patients with EUS abnormalities was 3.2 (1) years compared with 7.6 (4.7) years of ACPH duration in patients who underwent normal EUS ($P = 0.003$).

DISCUSSION

A long time has passed since Warshaw and Lee[14] in 1978 spoke about chronic hyperamylasemia as a "chemical oddity or a clinical entity." However, even if novel and substantial information has been acquired on this condition, what we today call ACPH was not a fully defined entity.[1,2,15,16] A proper diagnosis of ACPH is crucial not only because it reassures both physicians and patients that the condition is really benign but also because it can prevent further investigations or hospital admissions.[17] Moreover, adequate information regarding ACPH may help these subjects have a good quality of life and avoid psychological support.[18] The most important step in the management of ACPH is the patient's clinical history and a detailed physical and laboratory evaluation to assess possible pancreatic or extrapancreatic causes.[5]

We should be aware that there is no indication for measurement of serum lipase or amylase in patients having no abdominal pain.[18] Several practitioners usually prescribe these blood examinations as a part of routine checkup and once hyperenzimemia is

TABLE 1. Clinical Characteristics of the 73 Patients Studied

Characteristic	EUS (n = 45)	No EUS (n = 28)	Overall (N = 73)
Sex, n (%)			
Male	19 (42.2)	16 (57.1)	35 (47.9)
Female	26 (57.8)	12 (42.9)	38 (52)
Alcohol consumers (<40 g/d), n (%)			
No	28 (62.2)	10 (35.7)	38 (52)
Yes	17 (37.8)	18 (64.3)*	35 (47.9)
Smoking habit, n (%)			
No	24 (53.3)	11 (39.3)	35 (47.9)
Yes	21 (46.7)	17 (60.7)	38 (52)
Familial pancreatic hyperenzymemia, n (%)			
No	41 (91.1)	25 (89.3)	66 (90.4)
Yes	4 (8.9)	3 (10.7)	7 (9.5)
Age, mean (SD), y	62.4 (15.2)	53.0 (12.7)	58.7 (13.9)
BMI, mean (SD), kg/m^2	25.4 (2.8)	23.9 (3.1)	24.7 (3)
Amylase, mean (SD), U/L, (UNL 110 IU/L)	320 (406)	272 (268)	302 (349)
Lipase, mean (SD), U/L, (UNL 60 IU/L)	252 (459)	236 (196)	246 (378)

*Statistically significant.

UNL indicates upper normal limit.

TABLE 2. Endoscopic Ultrasonography Findings in the 45 Patients Who Underwent This Examination

EUS Findings	n (%)	Sex M/F	Age, Mean (SD), y	Serum Amylase, Mean (SD), IU/L	Serum Lipase, Mean (SD), IU/L	Previous Negative Examinations, %	Duration of ACPH, Mean (SD), y
No alterations	38 (84.4)	17/21	62.7 (16.1)	350 (436)	197 (216)	US, 86.8; CT, 34.2; MRCP, 52.6	7.6 (4.7)
Branch duct IPMN	3 (6.7)	0/3	66.7 (2.8)	174 (57)	225 (200)	US, 100; CT, 100; MRCP, 66.6	4.0 (1.0)
Duodenal diverticulum	1 (2.2)	1/0	71	135	2941	US, CT	3
Chronic pancreatitis	1 (2.2)	0/1	54	130	90	US, CT	3
Annular pancreas	1 (2.2)	1/0	43	137	35	US, CT	2
Undefined cyst	1 (2.2)	0/1	58	185	102	US, CT	3
Overall	45 (100)	19/26	62.41 (15.2)	320 (406)	252 (459)	US, 88.8; CT, 44.4; MRCP, 48.8	6.9 (4.6)

revealed, they require radiological examinations or refer these subjects to gastroenterologists with the erroneous suspicion of pancreatic disease.[18] On the other hand, EUS is now considered the most sensitive investigation to diagnose or exclude pancreatic diseases.[19]

The aim of this study is to assess whether the results of EUS may modify the management of patients with pancreatic hyperenzymemia. The study was retrospective and based on a consistent number of patients having long-lasting ACPH. Our results showed that EUS revealed abnormalities in subjects negative in previous examinations. In particular, a pancreatic cyst was found in 4 patients, 3 of them diagnosed as BD-IPMNs without worrisome features, and 1 undefined small cyst, probably another BD-IPMN. It has been reported that pancreatic hyperenzymemia may be present in 5% of patients with BD-IPMNs.[20] On the other hand, we have previously shown that approximately 7% of patients with ACPH developed an IPMN during follow-up.[6] Recent consensus guidelines recommended a diagnostic workup even in patients with small (<1 cm), asymptomatic, pancreatic cystic neoplasms.[21] Thus, an appropriate follow-up of ACPH using also EUS examination is warranted in these kind of subjects.

We also found that 1 duodenal diverticulum and 1 annular pancreas were detected by EUS. It is well known that juxtapapillary duodenal diverticulum may be associated with ACPH,[7] but the finding of ACPH in a subject having an annular pancreas is a new finding that we have previously described.[22]

In this study, we have detected 1 patient with EUS findings suggestive of chronic pancreatitis. In chronic pancreatitis, the fibrosis of the pancreatic tissue with consequent loss of exocrine function of the pancreas can result in normal or only slightly elevated serum enzyme levels, whereas high levels are usually found during symptomatic acute attacks of pancreatitis.[23,24] Endoscopic ultrasonography has become a useful and safe technique for detecting pancreatic parenchymal and ductal abnormalities suggestive of chronic pancreatitis.[12,25–28] Advantages include its ability to detect subtle pancreatic changes, not only parenchymal but also ductal abnormalities that are undetectable using other imaging modalities. Several investigators have reported EUS criteria for diagnosis and severity of chronic pancreatitis.[12,27–30] In 2009, Catalano proposed the so-called Rosemont classification as a standardized EUS diagnostic criteria for assessing chronic pancreatitis, with grouping of criteria into major and minor importance categories.[13]

In this study, no cases of pancreatic cancer were found in patients who were referred with ACPH. Our results showed that EUS allows detection of pancreatic diseases not shown by previous techniques. Nevertheless, the question is whether these findings cause pancreatic hyperenzymemia or hyperenzymemia is a biochemical anomaly not associated to the pancreatic malformation.[31,32] Indeed, it is not clear how these abnormalities can explain the high serum levels of pancreatic enzymes that can involve only 1 of these enzymes and that can present considerable over time fluctuation, including temporary normalization.[17,31] In our study, 15% of patients showed transient normalization of the abnormally elevated serum enzyme levels, including 3 of the 7 patients with EUS-detected abnormalities. It is important to note that the abnormalities revealed by EUS are more frequent in the first 3 years of ACPH duration, confirming our previous observations,[6] and that this could suggest a stricter diagnostic workup at the beginning of the diagnosis of ACPH.

In conclusion, EUS adds more useful information in approximately 15.5% of patients with ACPH. Usually, small BD-IPMNs without worrisome features that require follow-up are found at the beginning of the diagnosis of ACPH. Endoscopic ultrasonography has a role in the diagnostic workup of ACPH even if additional prospective studies are needed to assess the true role of this examination in ACPH subjects.

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