Pancreas divisum: evaluation with secretin-enhanced magnetic resonance cholangiopancreatography

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Background: The clinical significance of pancreas divisum (PD) remains controversial. Secretin-enhanced magnetic resonance cholangiopancreatography (S-MRCP) is a noninvasive diagnostic procedure that relies on the dynamic response of the main pancreatic duct (MPD) to secretin stimulation. The aim of this study was to determine the frequency of PD and to analyze the dynamic changes of the MPD by using S-MRCP in patients referred for suspected pancreatic diseases before ERCP.

Methods: MRCP was obtained before and at 30-second intervals over 10 minutes after secretin stimulation in consecutive patients with idiopathic acute pancreatitis (n = 67), persistent hyperamylasemia (n = 42), recurrent abdominal pain thought to be of pancreatic origin (n = 48), severe chronic pancreatitis (n = 68), and in a control group (n = 54).

Results: Thirty patients (10.8%) had a PD at S-MRCP. Secretin stimulation improved the detection of PD in 23% (7/30). The frequency of PD was not significantly different (p > 0.2) between these groups. The occurrence of an abnormal response at S-MRCP (persistent dilatation of the MPD) did not significantly differ in patients with or without PD (p > 0.4).

Conclusion: The frequency of PD did not differ between groups, and the dynamic changes of the MPD during S-MRCP were similar in patients with and without PD. (Gastrointest Endosc 2001;53:728-33.)

The frequency of pancreas divisum (PD) in western countries ranges from 4% to 14% in autopsic series and from 2% to 8% in ERCP series. It is essentially the absence of fusion between ventral and dorsal pancreatic ducts. Because the major part of the pancreatic secretion must flow through the minor papilla, PD could predispose to obstructive pancreatopathy, causing both pancreatitis and pancreatic-type pain, and be implicated in the development of severe chronic pancreatitis. These issues are still controversial and ERCP studies provide conflicting results, being limited by the fact that endoscopic access to the minor papilla is significantly more difficult to achieve than for the major papilla, a factor potentially responsible for selection bias in referral centers.

Magnetic resonance cholangiopancreatography (MRCP) is a diagnostic technique that allows noninvasive multiparametric visualization of the biliary and pancreatic ducts without injection of iodinated contrast material. This technique has been proved successful in identifying PD with an accuracy similar to ERCP. The use of fast MR technology and abdominal phased-array coils has made it possible to obtain high-resolution images of the biliary and pancreatic ducts within a few seconds. Under these conditions, dynamic studies of the pancreatic duct behavior after secretin stimulation (S-MRCP) have been proposed.

In the present investigation, patients in whom ERCP had never been attempted were studied with S-MRCP for 2 purposes: (1) to determine the frequency of PD in control subjects, in patients without abnormalities by CT or US but with suspected pancreatic disease (acute relapsing pancreatitis, persistent hyperamylasemia and lipasemia, pancreatic-type pain), and in patients with severe chronic pancreatitis (calcifications or ductal dilatation), and (2) to compare in each group the dynamics of pancreatic duct filling after secretin stimulation in patients with and without PD.
acute pancreatitis, defined as two or more episodes of pain attacks associated with an increase in serum lipase and amylase levels (group 1, amylases: 2-4.3 times the normal value [NV] [mean 2.5]; lipases: 1.5-5 times the NV [mean 3]), or persistent hyperlipasemia and hyperamylasemia (2 measurements at 1-month intervals) in the absence of pain\textsuperscript{14} (group 2, amylases: 1.5-10 times the NV [mean 4.3], lipases: 2-6 times the NV [mean 3]), or recurrent or persistent abdominal pain thought to be of pancreatic origin in the absence of serum pancreatic enzymes abnormality (group 3).

During the same period S-MRCP was performed in patients with severe chronic pancreatitis (with calcification or ductal dilatation) referred for endoscopic management (group 4) and in a control group of patients without any history of pancreatitis, pancreatic-type pain, or increase in serum levels of amylase or lipase referred for routine evaluation of biliary anatomy before laparoscopic cholecystectomy (group 5). ERCP was performed in all patients with severe chronic pancreatitis and whenever a PD was detected at S-MRCP.

All examinations were performed in accordance with the recommendations of our institutional board, and all patients gave informed consent after an explanation of the complete examination procedure. Because the prevalence of PD has been reported to be more than 6 times higher in patients referred after an unsuccessful ERCP,\textsuperscript{6} only those patients referred before any attempt at ductal opacification were considered.

**MR pancreatography**

The MR pancreatograms were acquired with a clinical 1.5T MR imager (Gyroscan ACS NT, Philips Medical Systems, Best, The Netherlands) by using a dynamic breath-hold two-dimensional single-shot turbo spin echo T2-weighted sequence as previously described.\textsuperscript{13} With this heavily T2-weighted sequence (echo time of 1200 ms)
a projectional image of the biliary and pancreatic ducts is obtained in 2.7 seconds without any need for further post-processing; the spatial resolution was 1 mm $\times$ 1.5 mm.

A set of images was acquired before secretin stimulation to enable optimal positioning of the imaged section in the coronal plane. Secretin (Secrelux, Goldham-Bioglan, Zusmarshausen, Germany) was administered in 1 minute at a dose of 1 clinical unit/kg of body weight. In accordance with studies of manometric response to secretin stimulation, acquisition of the optimal projection was repeated every 30 seconds after secretin stimulation, and this dynamic procedure was conducted over a period of 10 minutes. During the imaging procedure the patient was supine.

**Data analysis**

All MR images were analyzed at the MR imaging console by a radiologist (C.M.) and a gastroenterologist (J.D.), both with experience in biliopancreatic imaging who were unaware of the clinical and laboratory data. The diagnosis of PD was established at S-MRCP when the accessory pancreatic duct directly extended into the main pancreatic duct (MPD), crossing the common bile duct, and was separated from a smaller ventral duct. In all patients, the caliber of the MPD was measured at the level of the body of the pancreas with electronic calipers. Measurements were made before secretin administration and in all the time series images after secretin stimulation. Baseline, maximum, and final diameters of the MPD were recorded. Dynamic changes in the caliber of the MPD were considered normal when, after secretin stimulation, dilation of the MPD followed by a progressive return to the baseline diameter within 10 minutes was observed according to normal values previously defined (baseline: $2.3 \pm 0.5$, maximum: $3.1 \pm 0.7$, final: $2.2 \pm 0.5$, mean $\pm$ SD in mm$^{13}$) and when no other ductal abnormality was visualized. Taking into account the spatial resolution of 1 mm for our measurements, the pancreatic duct was considered abnormal at S-MRCP when the final MPD diameter was greater than 3 mm or whenever other landmarks of chronic pancreatitis were observed (ductal narrowing, presence of pseudocysts, or abnormal MPD branches).

**Figure 2.** Baseline, maximum, and final (at 10 minutes) main pancreatic duct caliber after secretin stimulation in groups 1-5 (mean value in mm, SD). **Black bars** represent patients without PD; **shaded bars** represent patients with PD (group 1: idiopathic acute pancreatitis, group 2: persistent hyperlipasemia and hyperamylasemia, group 3: persistent transfixed abdominal pain, group 4: severe chronic pancreatitis, group 5: control group).
Statistical analysis

The frequency of PD was compared between the different groups with the Fisher exact test. Because of the limited spatial resolution of the technique, a nonparametric analysis was performed with the Kruskal-Wallis test to compare the distributions of pancreatic duct calibers between groups and the Kolmogorov-Smirnov test to compare it within groups between patients with and without PD. The incidence of a normal response at S-MRCP was compared in each group between patients with and without PD with a Fisher exact test. A \( p \) value less than 0.05 was considered significant for a single test of hypothesis; for multiple testing the Bonferroni correction was applied.

RESULTS

Patients

Twenty-eight patients referred for S-MRCP after a previous unsuccessful ERCP were excluded (9 with acute pancreatitis, 5 with pancreatic-type pain, 4 with increased levels of serum amylase and lipase, and 10 with severe chronic pancreatitis). Among these, 14 patients (50%) had PD (9 with acute pancreatitis, 3 with pancreatic-type pain, and 2 with severe chronic pancreatitis). A total of 279 patients were included in the study (Table 1).

Imaging findings

Before secretin administration, the entire course of the MPD could not be fully evaluated in 45 of 279 (16%) patients. After secretin stimulation, it was completely displayed in all of them. At S-MRCP 30 patients (10.8%) had PD; in 7 patients (23%) the detection of PD was improved by secretin (Fig. 1). In group 4 (severe chronic pancreatitis) 7 patients had a final diagnosis of PD at ERCP, including one patient with PD that was not diagnosed by both reviewers at S-MRCP; in another patient secretin correctly ruled out the presence of PD. In the remaining groups, a total of 24 patients had PD, which was confirmed in all at ERCP.

The frequency of PD, assessed by S-MRCP, was not significantly different between the groups (Table 1). \( (p > 0.2) \) Assuming the actual proportions of PD to be 0.12 and 0.20, i.e., a difference of 8%, the type II error was about 0.76.) The frequency of PD was not statistically different in patients than in control patients (aggregated groups 1-4: 24/225 vs. group 5: 6/54; \( p = 0.94) \).

The MPD caliber variation under secretin stimulation in the different groups is summarized in Figure 2. Except for one, all patients in the control group had normal MPD calibers. One patient had a noncalcified stone in the distal common bile duct and no PD. As expected, the mean baseline, maximum, and final caliber of the MPD were significantly higher in the group of patients with severe chronic pancreatitis than in each of the other groups (\( p < 0.0001) \) (Kruskal-Wallis). The caliber of the MPD in patients with PD
was not significantly different than in patients without PD, with the exception of the severe chronic pancreatitis group, in which the final MPD caliber was smaller in patients with PD (nominal significance for a single test hypothesis: \( p = 0.047 \), correction of significance levels for multiple testing of data from individual subjects removes this significance).

The frequency of an abnormal response of the MPD to secretin stimulation (Fig. 3) is shown in Table 2 for all groups, except group 4 (severe chronic pancreatitis), in which all S-MRCP studies were abnormal. In the remaining groups, the frequency of an abnormal response was never found to be different in patients with or without PD. When all patients were considered, the frequency of an abnormal MPD behavior under secretin was higher in groups 1 to 3 than in control patients (nonsignificant after multiple testing correction).

**DISCUSSION**

The present study shows that in patients referred without any previous attempt at ERCP, the frequency of PD is similar in control patients, in patients with established chronic pancreatitis, and in patients in whom pancreatic disease is suspected on the basis of idiopathic pancreatitis, increased serum levels of pancreatic enzymes, or pancreatic-type pain. This suggests that recruitment bias, especially at tertiary centers to which patients are often referred after unsuccessful MPD opacification, may have resulted in an overestimation of the prevalence of PD in ERCP studies. Indeed, failure of endoscopic opacification of the pancreas is often related to the presence of a PD. This is further illustrated by the high frequency (50%) of PD found among patients referred after unsuccessful ERCP during the study period.
The accuracy of MRCP in the identification of a PD has been reported to be the same as that for ERCP. In the group of patients with severe chronic pancreatitis, the detection of PD at S-MRCP might be more difficult because of the presence of stones and strictures in either the ventral or dorsal pancreatic ducts. Nevertheless, in our study S-MRCP and ERCP findings correlated in 98.5% (67/68) of the cases of severe chronic pancreatitis.

The frequency of PD observed in all groups is slightly higher than the frequency previously reported in control patients in Western countries in endoscopic series, but is close to that reported in autopsy studies. This might be related to the fact that dynamic S-MRCP eliminates failure of ductal opacification. Indeed, in our study secretin improved the visualization of the pancreatic ducts in 16% of the patients and improved the detection of PD in 23%. With a systematic attempt at dorsal cannulation, the frequency of PD identification reached 9%.

The second major conclusion of this study is that the dynamics of pancreatic duct filling after secretin stimulation did not differ between patients with or without PD. In all but one control patient, secretin stimulation induced a transient increase in MPD caliber. Among patients with either idiopathic acute pancreatitis, persistent hyperlipasemia, and hyperamylasemia or even those with pancreatic-type abdominal pain, it has been possible to identify patients with persistent dilatation of the MPD. Interestingly, these findings were observed with a similar frequency in the 3 groups and this was not affected by the presence of a PD. This suggests that among these patients, it might be possible through this noninvasive test to identify a group of subjects that has either papillary (minor or major) obstruction to outflow or a lack of parenchymal compliance to account for the prolonged dilatation observed. In severe chronic pancreatitis, the reduction of pancreatic juice outflow and fibrosis dramatically reduces the compliance of the parenchyma, which is reflected by a significantly dilated MPD before stimulation and a poor response of the MPD to stimulation. Whether these observations are clinically relevant can only be established by a randomized study evaluating the effectiveness of treatment in patients with or without dynamic changes at S-MRCP.

In conclusion, this prospective study with S-MRCP demonstrated that the frequency of PD is similar in different groups of patients referred for evaluation of pancreatic symptoms and control patients and demonstrated the absence of an increased frequency of abnormal pancreatic response to secretin stimulation in patients with PD.

REFERENCES