Acute Relapsing Pancreatitis. Congenital Variants: Diagnosis, Treatment, Outcome

Myriam Delhaye, Celso Matos, Jacques Deviere

Erasme Hospital. Brussels, Belgium

Introduction

Congenital variants of the pancreas are seen in approximately 10% of the general population and include both malfusion variants such as pancreas divisum and malrotation variants such as annular pancreas and partial agenesis [1] (Figure 1). Most of these congenital variants are of limited clinical importance and are found incidentally at endoscopy, surgery, or autopsy.

Pancreas Divisum

Pancreas divisum (PD) is the most common anatomic variant of the human pancreas occurring in 5 to 10% of caucasian individuals and resulting from a failure of fusion of the dorsal and ventral pancreatic ducts during the second month of life in utero [2].

Diagnosis

The diagnosis of PD is classically based on endoscopic retrograde cholangiopancreatography (ERCP) showing the filling of a short and thin pancreatic ventral duct at the main papilla and the filling of a larger pancreatic dorsal duct at the minor papilla draining nearly the entire pancreas from the tail to the anterior part of the head without any connection to the ventral duct [3]. Recently, magnetic resonance cholangiopancreatography (MRCP) has been shown to

Figure 1. Congenital variants of the pancreatic ducts.
be an accurate tool in the diagnosis of PD with an accuracy similar to ERCP [4].

The diagnosis of PD by MRCP is established when the dorsal pancreatic duct has a constant caliber, crosses the common bile duct anteriorly and is separated from a smaller ventral duct [4, 5] (Figure 2).

Secretin stimulation has been proposed to improve pancreatic duct delineation by increasing the secretion of fluid and bicarbonate by the exocrine pancreas resulting in an increase of the liquid content of the pancreatic ducts [6]. Secretin acts as a hydrographic endogenous contrast agent and it is used routinely for the evaluation of patients with suspected pancreatic disease [6, 7]. This technique provides dynamic pictures of a higher quality and improves the detection of anatomic variants such as PD: the diagnostic accuracy becomes similar to that of ERCP only when dynamic secretin MRCP (S-MRCP) is used for detection [5].

It has been suggested that PD predisposes to an obstructive pancreatopathy as the major part of the pancreatic secretion must flow through the minor papilla [8]. However, most people with PD will never develop pancreatitis since PD occurs in about 5 to 10% of the population while the incidence of pancreatitis from all causes is only 0.1% [9].

Epidemiological studies, based on ERCP series, offer conflicting opinions supporting [8, 10, 11], or denying [2, 12, 13, 14] a putative role for PD in the pathogenesis of pancreatitis.

In our experience, the incidence of PD among various pancreatic and non-pancreatic diseases was not statistically different [3]. Some selection biases have been identified in order to explain the discrepancies between the reported series [3], the most important being the increased incidence of PD (39%) among patients referred after ERCP failure. Therefore selection of suspected idiopathic pancreatitis on the one hand, and of ERCP failures on the other hand, could falsely support an apparent association of PD and pancreatitis.

As most patients with PD do not develop pancreatitis, a stenosis of the minor papilla could be the additional necessary factor to cause an acute problem in a minority of PD patients.

The objective assessment of stenosis of the minor papilla is difficult; resistance to passing probes through the minor papilla at the time of surgery is invasive and obsolete [15], success or failure of endoscopic cannulation of the minor papilla or measurement of the emptying time of the dorsal duct after pancreatography have not been standardized [3], manometric studies showing an increase in the pancreatic dorsal duct pressure are of limited usefulness [16] and normal values have not been defined for the minor papilla [17].

Prolonged dilatation of the pancreatic dorsal duct visualized at ultrasound for more than 15 minutes after i.v. secretin injection (US-secretin test) has been claimed to be a useful objective test of stenosis of the minor papilla [18]. However, other authors were not able to reproduce these results [19]. Limitations of the US-secretin test include the ability to see the main pancreatic duct (obesity, overlying gas) and the reliability and reproducibility of measurement of millimetric changes in duct caliber on ultrasonography. Normal values for dynamic changes in the caliber of the main pancreatic duct were previously defined on MRCP after secretin stimulation [6]. During the first minutes after secretin administration, the main pancreatic duct undergoes
enlargement (maximum diameter is reached after 2-3 minutes) which is followed by a return to almost equal its baseline diameter at 10 minutes, as pancreatic juice fills the duodenum. In a prospective study including 279 patients investigated by S-MRCP and involving 67 patients with idiopathic acute pancreatitis, 42 patients with persistent hyperamylasemia and hyperlipasemia in the absence of pain, 48 patients with recurrent or persistent abdominal pain thought to be of pancreatic origin in the absence of serum pancreatic enzymes abnormality, 68 patients with severe chronic pancreatitis (with calcifications or ductal dilatation) and 54 control patients referred for routine evaluation of biliary anatomy before laparoscopic cholecystectomy, the frequency of PD was not significantly different between these groups (10.4%, 11.9%, 12.5%, 8.8% and 11.1%, respectively) [5]. PD was confirmed in all cases at ERCP. An abnormal response at S-MRCP was defined as a persistent dilatation of the main pancreatic duct greater than 3 mm at 10 minutes after secretin injection. An abnormal response can be identified in patients with either idiopathic acute pancreatitis, or persistent hyperamylasemia and hyperlipasemia or persistent pancreatic pain with a similar frequency in those 3 groups (11.9%, 14.3% and 6.2%, respectively) suggesting a papillary obstruction to outflow or a lack of parenchymal compliance in some of these patients. Nevertheless, the major conclusion of this study is that the occurrence of an abnormal response at S-MRCP did not significantly differ between patients with or without PD despite the specific group to which they belonged [5].

Another argument frequently seen for PD being involved in the pathogenesis of pancreatitis is the presence of morphological changes confined to the dorsal pancreatic duct [20, 21]. However, in a recent study performed by our group [22], a majority of patients with PD and chronic pancreatitis had typical ductal abnormalities involving the ventral duct (74%) at presentation and even isolated ventral duct alterations were observed in 14% of the cases. Moreover, after a mean follow-up of 44 months, 83% of patients studied with isolated ventral pancreatitis developed alterations of the dorsal ductal part of the gland, suggesting that ductal anatomic factors play a marginal role in the manifestation of this pancreatic disease.

**Treatment Options**

In spite of controversies with regard to the clinical relevance of a potential stenosis of the minor papilla, several endoscopic and/or surgical procedures have been proposed in an attempt to improve the pancreatic outflow through the minor papilla. The selection criteria for patients with PD who might benefit from therapy at the level of the minor papilla is still not clearly defined. However, most authors acknowledge the fact that results are better when the indication for treatment used is that of recurrent acute pancreatitis as compared to that used for patients with pain alone or chronic pancreatitis [reviewed in 17]. Surgical treatment consists of transduodenal sphincteroplasty of the minor papilla sometimes associated with cholecystectomy and major papilla sphincteroplasty making interpretation of the results somewhat confusing [9, 23]. Endotherapy options include endoscopic sphincterotomy of the minor papilla using a wire-guided standard sphincterotome or a needle-knife cutting along a previously inserted 5F or 7F guiding stent which is removed after a few days [24]. The orifice of the minor papilla can also be opened by dilatation using a 5-10F dilating catheter having a tapered tip or a balloon with a small diameter (4-5 mm) but it is not recommended because the results are short lived and dilatation may provoke ductal disruption and pancreatitis [17, 25].

Finally, stenting of the pancreatic dorsal duct has also been proposed either as a therapeutic
trial for patients who are having daily pain or as a long-term treatment [26, 27].

**Treatment Outcomes**

About 200 patients were included in 11 surgical series of minor papillary therapy from 1982 to 1996 [reviewed in 9 and 17]. The largest series, published by Warshaw et al. [23] included 88 patients and showed a high correlation between the results of the US-secretin test and the results of the therapy, namely that 92% of patients with an abnormal test had a beneficial outcome but only 40% of those with a normal test. Multivariate analysis showed that the mode of presentation (acute recurrent pancreatitis versus chronic pain) and the US-secretin test results were independently significant predictors of outcome. However, confirmation of these results has not been provided by other centers. Overall, after a mean follow-up of 29 months, the percentage of patients with recurrent acute pancreatitis who improved after surgical sphincteroplasty was 83% ranging from 70 to 100% as compared to 59% (0-100%) for patients with pain alone [17]. Major complications were reported in 4% and mortality in 0.5%. The restenosis rate was 8%.

The overall reported response rate to minor papilla endoscopic sphincterotomy mirrors the surgical results in similar patient categories [17]. In 5 series with a total of 83 patients who were studied from 1984 to 1993, 74% of the patients with recurrent acute pancreatitis improved as compared to 26% of patients with pain alone and 46% of patients with chronic pancreatitis. One death was reported after failure of minor papilla cannulation complicated by severe acute pancreatitis and development of a pancreatic abscess [24]. The follow-up was limited in most series ranging from 3 to 24 months. The restenosis rate was estimated to be 10-20%. The risk of secondary stenosis due to scarring could probably be lowered with use of pure cutting current alone. Interestingly, it was reported that the long-term outcome could be predicted by the patient's clinical status within 6 months of treatment and that repeated endoscopic therapy in those failing the initial minor papilla endoscopic sphincterotomy did not appear to be useful [24].

In the only randomized controlled trial [26], 19 patients with PD and at least 2 documented episodes of idiopathic pancreatitis were randomized to either dorsal duct stent placement (n=10) or controls (n=9). The stents were changed every 3-4 months for 1 year. Nine of the 10 stented patients benefited clinically, as compared with only 1 of the 9 controls, over a mean follow-up period of 24 months.

From 1994 to 2000, 4 additional series were published (2 prospective, 2 retrospective) on endoscopic pancreatic stenting of the pancreatic dorsal duct in patients with PD and acute recurrent pancreatitis [reviewed in 27] with a total of 66 patients followed for about 24 months with improvement reported in 75% of the cases.

Potential adverse effects of pancreatic stenting include stent occlusion or migration, and induction of ductal and parenchymal changes when the stent is implanted in a normal pancreatic duct as it is the case in acute recurrent pancreatitis without morphological changes of the pancreatic ductal system. Up to 84% of the patients were reported to have iatrogenic ductal abnormalities induced by the stent which are only partially reversible after stent removal [27].

When considering the absence of strict selection criteria that indicate which patients would be most amenable for endoscopic or surgical therapy, the absence of consensus regarding the best therapeutic approach because of missing randomized trials directly comparing management strategies and the unforeseeable complications resulting from endoscopic or surgical procedures on the minor papilla, future randomized studies evaluating the effectiveness of treatment in patients with or without dynamic changes suggesting papillary obstruction at S-MRCP or US-secretin test are required to establish the clinical relevance of minor papillary
stenosis in a defined group of patients with PD and acute relapsing pancreatitis. Until more convincing data indicate clearly defined management strategies, a cautious and conservative attitude should be observed in this category of patients.

**Other Congenital Variants**

*Anomalous pancreaticobiliary union (APBU)* is a congenital malformation of the pancreaticobiliary tree in which the confluence of the common bile duct and the pancreatic duct is outside the duodenal wall, with a common channel measuring more than 15 mm [28]. APBU is rare, with an incidence ranging from 1.5 to 3.2% and results from the uneven proliferation of the bile duct epithelium during fetal life [29]. This anomaly has been postulated as a possible cause of choledochal cysts, bile duct and gallbladder carcinoma, and recurrent pancreatitis [28, 30, 31].

The pathogenesis of recurrent pancreatitis in cases of APBU has been associated with temporary occlusion of pancreatic secretion by stones, protein plugs, or sphincter of Oddi dysfunction [32] leading to a rise in pancreaticobiliary intraductal pressure. In one series [31], acute pancreatitis was reported in 31% of APBU patients (20/64) in association with a choledochal cyst in 14 of them. For the most part, acute pancreatitis was mild and resolved in a few days with conservative treatment.

*Choledochocele*, a Type III choledochal cyst according to the Todani classification [33], represents less than 2% of all choledochal cysts [34] and is described as being a dilatation of the intraduodenal segment of the common bile duct. It is also associated with recurrent pancreatitis [35] by creating an intermittent obstruction to the pancreatic duct when it becomes distended with bile.

In *duodenal duplication*, a cyst-like structure bulges into the duodenal lumen just distal to the papillary orifice. It must be differentiated from the choledochocele which is located proximally to the papilla and covered with biliary mucosa. The association of pancreatitis with duodenal duplication is infrequent [36, 37]. Pancreatitis may result from occlusion of the pancreatic ductal system by the distended duodenal cyst filled with secretions or stones.

**Diagnosis**

The gold standard for diagnosis of these anatomical variants is ERCP [38]. However ERCP in patients with APBU has been associated with a particularly high risk of pancreatitis [39] probably related to the fact that in the presence of a common channel, cyst opacification often requires repetitive injections of the pancreatic duct. MRCP was found to have the capability of detecting APBU in 82% of cases provided that a common channel 15 mm or longer was evidenced [40] (Figure 3). In 2 patients with APBU and a mild fusiform dilatation of the common bile duct, we were able to demonstrate in vivo, by using S-MRCP, the pancreaticobiliary reflux as shown by progressive gallbladder enlargement after secretin injection without duodenal filling [41].

![Figure 3](image_url)

Figure 3. A 48 year old woman presenting with an 8 year history of recurrent acute pancreatitis. MRCP demonstrates a long common channel as well as the fusiform cystic dilatation of the common bile duct (Type I choledochal cyst according to the Todani classification).
Endoscopic ultrasonography (EUS) can also detect APBU in 88% of cases if a common channel of 12 mm or longer is observed [42]. However, EUS is quite invasive and is limited by the fact that it cannot adequately demonstrate the whole common channel, common bile duct and main pancreatic duct on the same scanning plane [42].

In duodenal duplication, ERCP provides accurate information about the exact location, size and communication with the pancreatic and biliary tract [43]. However, dynamic MRCP with injection of secretin can also depict the normal bile duct and pancreatic duct while the cyst itself is seen as a bright spot impinging on the duodenal lumen surrounded by a dark rim (Figure 4). Furthermore, these images are quite clear.

**Treatment Options and Outcomes**

The treatment of choice for APBU with a congenital choledochal cyst is surgical excision of the extrahepatic bile duct and gallbladder with Roux-en-Y reconstruction of the biliary tree [44]. For patients with APBU without a congenital choledochal cyst, prophylactic cholecystectomy is recommended because of the higher risk of gallbladder carcinoma development [30].

Endoscopic therapy has also been proposed in APBU patients in an attempt to decrease resistance at the papilla and preclude pancreaticobiliary reflux. Whether such therapy, when performed at an early stage, can prevent the development of choledochal cysts or subsequent biliary malignancy remains unknown. Endoscopic biliary sphincterotomy has proven to be beneficial in 10 out of 11 patients presenting with APBU and relapsing acute pancreatitis [45].

Management of choledochocele by endoscopic biliary sphincterotomy and removal of common bile duct stones, when present, is a currently accepted therapy with excellent long-term results [38, 46].

The surgical approach in duodenal duplication cysts includes classic duodenotomy and marsupialization to the adjacent duodenum [47]. Endoscopic drainage using either a papillotome [43] or a needle-knife sphincterotome [48] or a snare resection [49] has been described in the literature.

Three cases of duodenal duplication cysts were treated in our department by endoscopic snare resection in 1981, 1993, 1996 with excellent clinical and endoscopic long-term follow-ups without any symptomatic recurrence.

**Conclusions**

Congenital variants of the biliopancreatic ductal system provide interesting challenges when discovered during the diagnostic work-up of idiopathic acute recurrent pancreatitis. However most of these variants are clinically irrelevant. Methods for the selection of patients most likely to benefit from invasive therapy need to be refined. New developments in dynamic imaging procedures should provide the tools for achieving these objectives in the near future.

**Key words** Cholangiopancreatography, Endoscopic Retrograde; Choledochal Cyst; Duodenum: abnormalities; Image Enhancement; Magnetic Resonance Imaging; Pancreas: abnormalities; Pancreatic Ducts: abnormalities; Pancreatic Diseases: congenital; Pancreatitis: etiology; Recurrence; Secretin: diagnostic use;
Abbreviations

APBU: anomalous pancreaticobiliary union; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasonography; MRCP: magnetic resonance cholangiopancreatography; PD: pancreas divisum; S-MRCP: secretin magnetic resonance cholangiopancreatography

Correspondence

Delhaye Myriam
Medicosurgical Department of Gastroenterology
Erasme Hospital
Route de Lennik, 808
B-1070 Brussels
Belgium
Phone:+32-2-555.3712
Fax: +32-2-555.4697
E-mail address: mydelhay@ulb.ac.be

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