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Pancreas divisum: a reemerging risk factor for pancreatic diseases

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Pancreas divisum (PD) is the most common developmental anatomic variant of pancreatic duct. The attention towards the PD has grown significantly since there are reports that this condition may cause acute relapsing pancreatitis, chronic pancreatitis and chronic abdominal pain syndrome. Furthermore, over the years, there have been multiple reports of PD associated with different types of tumors. There is evidence that PD can be associated with pancreatic tumors (up to 12.5% of cases). The golden standard for diagnosing PD is endoscopic retrograde cholangiopancreatography, but since it is an invasive procedure magnetic resonance cholangiopancreatography with secretin is a good alternative. In case the patient is symptomatic, endoscopic or surgical treatment should be performed. This review describes the key points of the pathophysiology, diagnostic modalities, risks of pancreatitis and tumors, as well as treatment options of PD.

Keywords: acute relapsing pancreatitis; pancreas divisum; pancreatic tumors.

INTRODUCTION

The first person who described the pancreas was Claudius Galen (129-199) who provided the first description of the pancreas considering that its function is limited to being a cushion for the stomach. Johann Georg Wirsung (1589-1643) of Augsburg was the first scientist who discovered a ductal system in the pancreas and, until the rest of his life, he tried to find the answer to its function. Giovanni Domenico Santorini (1681-1737) of Venice made the next step in the description of ductal anatomy. He performed several hundred dissections of the pancreas and duodenum and then examined them using a magnifying glass. The results of his study showed that, frequently, the pancreas had a second accessory duct, which is named after him [1].

Pancreas divisum (PD) is the most common developmental anatomic variant of the pancreatic duct [2]. For the first time it was mentioned in the 17th century, but its description is attributed to Joseph Hyrtl (1810-1894) [3]. Later on in 1903, Eugene L. Opie (1873-1971) precisely described this anatomical variant and was the first to report that in post mortem examinations. PD is encountered in 10% of cases [4, 5]. Still even though it is the most widely encountered anatomic variant, PD is mentioned only in approximately 14% of the anatomy plus embryology books and in 70% of the surgery plus pathology books [6].

There is growing evidence that pancreatic ductal anomalies (PD, ansa pancreatica, meandering main pancreatic duct) are linked with pancreatic diseases [7-10]. The attention towards the PD has grown significantly since there are reports that this condition may cause acute relapsing pancreatitis (ARP), chronic pancreatitis (CP) and chronic abdominal pain (CAP) syndrome [11]. The current data indicates that the recurrence rate of acute pancreatitis can be up to 80% in patients with pancreaticobiliary malformation [12]. There are other malformations such as congenital cystic dilatation of the common bile duct which are also linked to this condition [7]. With all of this in mind, PD reemerges as risk factor in pancreatic diseases.

EMBRYOLOGY AND PATHOPHYSIOLOGY

In the normal pancreas, the Wirsung's and Santorini ducts have connections (figure 1). PD is a developmental anomaly, which represents the absence of fusion between the dorsal (Santorini) and ventral (Wirsung) pancreatic ducts. In such cases, the dorsal duct drains most of the pancreas and there-

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fore it has the role of the main pancreatic duct [13]. The abnormal fusion causes abnormal drainage of the majority of the pancreatic juice into the minor papilla and the minority (about 10%) through the major papilla [14, 15]. Furthermore, in patients with pancreas divisum, intraductal pressure can be elevated and this may persist during the fasting state [16]. Among other causes of pancreatitis, a stenosis of the accessory papilla of Santorini can be coexistent in pancreas divisum [17, 18]. Two common features are of particular importance in this anomaly. The first is ductal stenosis either at its ampullary outlet or at the junction part of the ducts of the pancreas. The second is a localized ductal ectasia, particularly in the uncinate process that is commonly associated with ampullary stenosis [18].

PD models were also tested in animals. In a PD canine model a group of dogs were divided into subgroups. The group I in which the communicating branch that connects the dorsal and ventral pancreatic ducts was partly ligated, the group IIa in which the connecting branch was amputated and completely ligated and the group IIb in which the dorsal duct was amputated and then ligated. The pancreas tissue was evaluated under light microscopy. In group IIb there was fibrosis with destruction of acini with evidence of inflamemation in the dorsal and ventral pancreas. Similar results were seen in Groups I and IIa but only in the ventral pancreas. Furthermore, there was a decrease in zymogen granules, swollen mitochondria and endoplasmic reticulum dilatation in the ventral pancreas of Groups I and IIa and the dorsal and ventral pancreas of Group IIb. Thus, the experimental canine model demonstrated that the pathogenesis of this condition is the functional obstruction of the minor papilla at the peak stage of secretion and PD can be an etiological factor for pancreatitis [19].

PD is usually asymptomatic, but recent data indicates that there may be links between PD, chronic abdominal pain (up to 60%) and idiopathic pancreatitis (up to 30%) [13]. Nevertheless, not all specialists agree that it may be a risk factor for pancreatitis and other authors state that it does not modify the course of the disease in some of the types of pancreatitis [20, 21].

INCIDENCE AND CLASSIFICATION

PD incidence is different and depends on the investigated population and the methods used. It can be diagnosed in 5-11% by magnetic resonance cholangiopancreatography (MRCP) [22-25], 9-16.8% secretin MRCP [23, 24, 26], 0.47-2.3% endoscopic retrograde cholangiopancreatography (ERCP) [27, 28], 13.6% by endoscopic ultrasound (EUS) [29], 4-14% autopsy [27, 30]. Besides, the overall endoscopic detection rate for PD seems to be higher in some parts of the world. For example, endoscopic detection rate for PD was 5.8% in the USA, 6.0% in Europe and only 1.5% in Asia [31].

PD can be classified in three main types [18]:

- Type 1 (classic PD) is the complete failure of fusion of the ducts of Santorini and Wirsung 70%. It can be further divided into two subtypes. The first subtype – the main pancreatic duct drains into the duct of Santorini (figure 2). The second (atypical or inverted PD) – the main pancreatic duct drains in the Wirsung's duct (figure 3).
- Type 2 is the absence of the duct of Wirsung 20-25%
- Type 3 (incomplete PD) is the presence of a small connection between the dorsal duct and the ventral duct 5-6%.

Table 1
Diagnostic test for PD

Test	Sensitivity	Specificity	General comments
S-MRCP	67-84.5%	88.1-96.8%	Misdiagnosis of PD can be in case of:
MRCP	60-72.2	76.2-93.8%	– presence of pancreatic necrosis
MDCT	57.1-83.3%	39.3%	– changes due to acute or chronic pancreatitis
EUS	86.7-95%	97%	– use of suboptimal technique
			– inexperienced examiners
			– presence of a loop in the main duct or other anomalies
			– presence of ductal strictures

MRCP – magnetic resonance cholangiopancreatography, S-MRCP – magnetic resonance cholangiopancreatography with secretin, MDCT – multiple detector computed tomography, EUS – endoscopic ultrasound

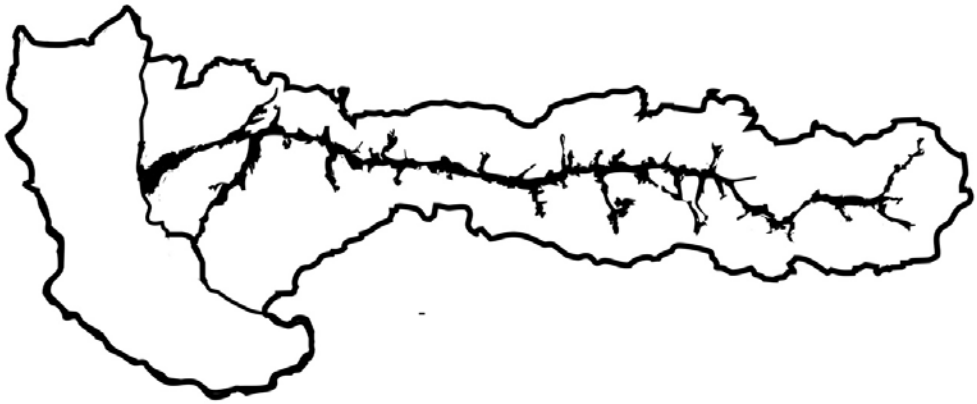

Figure 1. Normal pancreatic duct morphology.

Figure 2. Classical pancreas divisum.

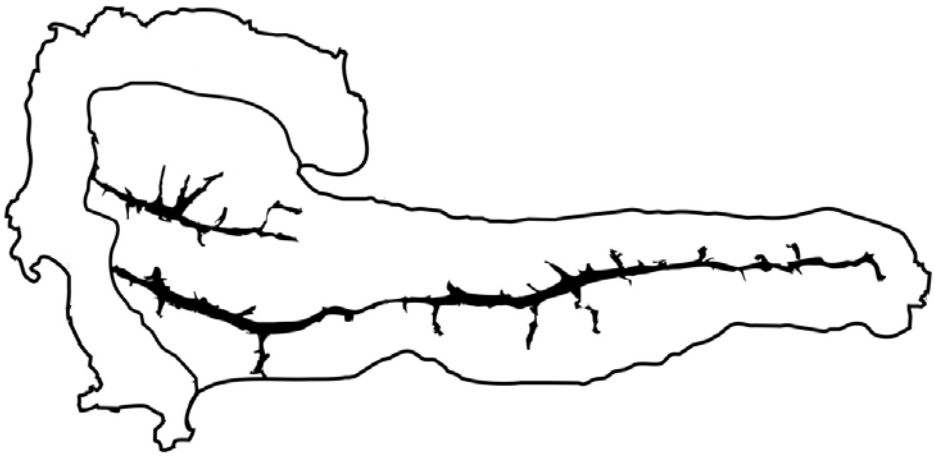

Figure 3. Atypical or inverted pancreas divisum.

DIAGNOSTIC POSSIBILITIES AND ASSOCIATED RISKS

Several diagnostic modalities have been developed over the years with different sensitivity and specificity to diagnose PD.

ERCP is considered the golden standard for diagnosing PD but is an invasive procedure. It was developed in 1968 and has become a widely used imaging technique in the diagnosis of pancreato-biliary diseases. ERCP provides a radiological image of the morphology and the pathological changes of

the pancreatic ducts and biliary tree. This image is obtained by the injection of a contrast agent into the main pancreatic duct and common bile [32]. Nowadays, due to the availability of modern noninvasive imaging modalities such as abdominal ultrasound (AUS), computed tomography (CT), MRCP and EUS (Table 1) ERCP has transformed from a diagnostic technique to mostly a therapeutic procedure [26, 29, 33-39].

The most frequent complications of ERCP are pancreatitis (1-7%), perforation (0.1%–0.6%) and bleeding (1-2%) [40, 41]. Other complications include infections (1.44%), cardiovascular and/or analgesia-related complications (1.33%), and although rare (0.07-0.08%) fatalities can also occur [42, 43]. The rate of complications depends significantly on the experience of medical personnel and whether they are performed in high-volume advanced centers [43]. The rate post-ERCP complications in children are around 4-10% [44, 45]. On multivariate analysis, pancreatic duct cannulation is associated with pancreatitis (OR 3.48). Moreover, in the same study age less than 4 years (10.7), male gender (12.8), and precut sphincterotomy (31.3) were associated with hemorrhage (all $p < 0.05$) [45]. Nevertheless others report that there are no significant differences between the underaged and the adult groups in terms of complications and longterm follow-up results [46].

However, it seems that this risk is higher in case of PD. One of the large retrospective studies on ERCP performed in patients with PD from 1997 to 2010 demonstrated that early complications occurred after 7.8% of procedures. These complications included post-ERCP pancreatitis in 6.8%, hemorrhage in 0.7%, perforation in 0.2%, cholecystitis in 0.1%, and cardiorespiratory complications in 0.1% of cases. Post-ERCP pancreatitis was uncommon in patients who did not have dorsal duct cannulation and occurred in 1.2% of procedures. In case of dorsal duct cannulation the rate of post-ERCP pancreatitis increases to 8.2% ($p < 0.01$). When cannulation with minor papilla sphincterotomy was performed the rates of post-ERCP pancreatitis increased even higher to 10.6% ($p < 0.01$). Multivariate logistic regression analysis demonstrated that significant predictors of post-ERCP pancreatitis included several factors: age < 40 (OR 1.8; 95% CI, 1.27-2.59), female sex (OR 1.94; 95% CI, 1.25-3.01), previous post-ERCP pancreatitis (OR 2.02; 95% CI, 1.32-3.1), an attempt for dorsal duct cannulation (OR 7.45; 95% CI, 3.25-17.07), and minor papilla sphincterotomy (OR 1.62; 95% CI, 1.05-2.48). Interestingly, the presence of severe chronic pancreatitis seemed to be a protective factor (OR 0.46; 95% CI, 0.22-0.98) [47].

Although ERCP is considered the golden standard of diagnosis, several studies demonstrated that there is a significant correlation between MRCP and ERCP in terms of detecting pancreatic diseases [48, 49].

MRCP is a diagnostic technique that produces high-quality images of the pancreatobiliary tree. There are several advantages which include its noninvasiveness; no complication, no radiation and no contrast agent. As a result, it causes less discomfort for the patients, and provides a large amount of information about the surrounding organs [50]. The injection of secretin (S-MRCP) which causes temporary dilation of the pancreatic ducts, principally by increasing pancreatic exocrine secretions, can further improve MRCP detection of the ducts and characterization of pancreatic disorders, allowing to asses the exocrine pancreatic reserve [51]. A recent meta-analysis based on 16 studies has demonstrated that the sensitivity and specificity for MRCP diagnosis of PD was 0.59 (95% CI 0.45 to 0.71) and 0.99 (95% CI 0.96 to 1.00). Compared to MRCP the sensitivity of S-MRCP was higher (0.83 [95% CI 0.66 to 0.92]) with the same sensitivity and specificity (0.99 [95% CI 0.96 to 1.00]) [52].

Finally, EUS is another widely used procedure for the visualization of the pancreas, which developed as an alternative for transabdominal ultrasonography, where intervening air does not permit good visualization of the organ [53]. The sensitivity and specificity for EUS was 0.85 (95% CI 0.67 to 0.94) and 0.97 (95% CI 0.90 to 0.99), respectively [52].

PD AND PANCREATITIS

The idea of PD being a risk factor for pancreatitis has been discussed for many years [54, 55]. Cotton in 1980 noted that in 169 patients with primary biliary tract PD was seen 3.6%. Among 78 patients with unexplained recurrent pancreatitis, the incidence was 25.6% [56]. In 18.8-20 % of patients who have idiopathic pancreatitis the only finding on ERCP was PD [57, 58]. Moreover, it seems that patients with ARP also have PD more frequently ($p = 0.004$) [59]. Some authors support the theory that isolated dorsal pancreatitis may be the predominant form [60]. The prevalence of CP in patients who have complete or incomplete PD is significantly

higher compared to controls ($p < 0.001$ and $p = 0.001$, respectively). Moreover acute pancreatitis occurs more frequently only in patients with complete PD ($p = 0.01$) [61]. It seems that PD can be the sole etiology of acute or chronic pancreatitis or require another factor (such as alcohol abuse), for its development [62].

There are no gender preferences, but there are genetic basis for PD [63]. Patients with PD are more likely to have mutations that cause predisposition for pancreatitis (27% *vs* 14%, $p = 0.0007$) [64].

The frequency of PD is higher in patients who have CFTR gene-associated pancreatitis compared to those with idiopathic and alcoholic pancreatitis ($p < 0.0001$). CFTR gene is of particular interest since PD is seen less frequently in SPINK1 and PRSS1 gene-associated pancreatitis ($p < 0.02$) [65]. Nevertheless, gene mutations may be the main factor but more probably are a co-factor in causing pancreatitis in this group of patients [66]. Some of the mutations of the SPINK1 gene cause a more severe clinical course and strong association of early-onset type of patients with idiopathic pancreatitis [67, 68].

It seems that the frequency of abnormalities of the main pancreatic duct, side branch dilatation, and pancreatic cysts are significantly different between the PD group and the non-PD group ($p = 0.122$; $p = 0.152$; $p = 0.741$). But there was no association between PD and pancreatic exocrine function ($p = 0.367$) [35]. Nevertheless, there are reports of complications such as cystic dilatation of the dorsal pancreatic duct [69], obstruction at the minor papilla [70], obstructing pseudocyst of the duct of Santorini [71]. There are also case reports that indicate that PD may be associated with other anomalies [72].

Finally, there is also data about drug-induced acute pancreatitis in patients with PD although no large studies have been conducted to prove whether PD is associated with drug-induced pancreatitis [73].

PD AND TUMORS

Over the years, there have been multiple reports of PD associated with different types of tumors [74-77]. There is evidence that PD can be associated with pancreatic tumors (up to 12.5% of cases). It is presumed that the pancreatic duct obstruction, which is caused by relative stenosis of the minor duodenal papilla, can lead to oncogenesis [78].

In one of the retrospective single-center studies, a total number of 118 cases of complete PD and 7850 cases of fused pancreas were identified with ERCP examinations. The prevalence of tumors was higher in PD group for pancreatic cancer (10% *vs* 4.8%), intraductal papillary mucinous neoplasms (5.1% *vs* 2.6%) and other pancreatic tumors (2.5% *vs* 1.1%) ($p = 0.008$; OR, 2.24). The percentages of PD patients with pancreatic cancer who had pain and elevation of serum pancreatic enzymes were significantly higher than among the PD patients without pancreatic cancer. Thus, the conclusion was that patients with PD, especially those who have pancreatic-type pain and elevation of pancreatic enzymes, should be followed up due to their risk of developing pancreatic cancer [79].

On the other hand, the incidence of biliary tract cancer was lower in patients with PD compared with fused pancreas (0.8% *vs* 5.3%, $p = 0.031$) [79]. Kamisawa and coworkers report that in concomitant pancreaticobiliary maljunction and incomplete PD the incidence of cancer of the biliary tract may be lower. The explanation was that the pancreatic juice reflux into the bile duct is reduced by the flow of pancreatic juice into the duodenum through the dorsal duct [80]. Another study finds that both pancreatic and biliary tumors are more frequent in patients with PD than in those with a dominant ventral duct ($p = 0.0383$) [81].

Nevertheless, it is worth mentioning that dilatation of the dorsal pancreatic duct is sometimes observed in cases of PD without the presence of tumors. In these cases there is pancreatic duct stenosis and additional examinations are required in order not to overlook a malignant process [82].

MANAGEMENT OF PD

Although PD can present with clinical symptoms it also can be asymptomatic [13]. Treatment is indicated in case of CAP, ARP or CP. The two main types of treatment for PD are endoscopic and surgical.

Endoscopic interventions include minor papillotomy, endoscopic stenting, and balloon dilation of the minor papilla. A recent meta-analysis demonstrated that the rate of improvement after endoscopic therapy varied significantly across studies, ranging from 31 to 96%. The pooled efficacy rate was 67.5% (95% CI 0.610-0.734; $p = 0.0001$). On subgroup analysis, patients with ARP had better endoscopic outcomes (pooled efficacy rate 76%,

95% CI 0.712-0.803, p = 0.0001). Dorsal duct stenting and longer follow up were the only parameters predictive of successful therapy. The pooled rate of pancreatitis after endoscopic retrograde cholangiopancreatography was 10.1% (95%; CI 0.084-0.124; p = 0.0001) [83].

Endoscopic treatment seems to depend on the underlying condition. A systematic review of case series and case-control studies demonstrated that the efficiency for ARP was 43% to 100% (median 76%) whereas for CP 21% to 80% (median 42%) and for CAP 11%-55% (median 33%). Despite endoscopic therapy, patients with PD still have relapse rates of 50% (95% CI, 35 to 68%) [84]. Nevertheless, after endoscopic stenting the overall pain level and number of hospital admissions decreased significantly. The use of pain medication reported by the patients was decreased in 58% of patients, 21% remained the same, and increased in 13% of cases. There was also improvement in symptoms like nausea (67%), vomiting (63%), and chronic pain (75%) [85]. In case of failure, there is a number of surgical procedures that can be performed (accessory duct sphincteroplasty alone or in combination with major sphincteroplasty and septoplasty, pancreaticojejunostomy, duodenum-preserving resection of the pancreatic head, cholecystectomy) [86-89].

Finally, a recent systematic review, which included 56 observational studies (31 endoscopic and 25 surgical studies), demonstrates that surgery was superior to endoscopic treatment. Surgery had a higher success rate (72% *vs* 62.3), lower complication rate (23.8% *vs* 31.3%) and lower re-intervention rate (14.4% *vs* 28.3%) compared to endoscopy [90].

CONCLUSIONS

PD is the most frequently encountered anomaly of the pancreatic ducts. The current evidence demonstrates that it is associated with several conditions like ARP, CP and CAP. The golden standard for diagnosing PD is ERCP but since it is an invasive procedure S-MRCP is a good alternative. In case the patient is symptomatic, endoscopic or surgical treatment should be performed. A high index of suspicion of PD should be present in case of patients with ARP, CP. CAP as well as idiopathic pancreatitis.

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Pancreas divisum (PD) este cea mai comună variantă de dezvoltare anatomică a ductului pancreatic. Atenția față de PD a crescut semnificativ, deoarece sunt rapoarte că această afecțiune poate provoca pancreatită acută recurentă, pancreatită cronică şi sindrom de durere abdominală cronică. Mai mult, de-a lungul anilor, au existat mai multe rapoarte despre PD asociat cu diferite tipuri de tumori. Există dovezi că PD poate fi asociat cu tumori pancreatice (până la 12,5% din cazuri). Standardul de aur pentru diagnosticarea PD este cholangiopancreatografia endoscopică retrogradă, dar, din cauză că este o procedură invazivă, rezonanța magnetică în regimul colangiopancreatografia cu secretină este o alternativă mai bună. În cazul în care pacienții sunt simptomatici, trebuie efectuat un tratament endoscopic sau chirurgical. Această revizuire descrie punctele-cheie ale fiziopatologiei, modalitățile de diagnosticare, riscurile de pancreatită şi tumori, precum şi opțiunile de tratament ale PD.

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