

## Pancreas Divisum and Pancreatitis

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### Problem

One of the biggest controversies in Pancreatology is whether Pancreas Divisum (PD) is the cause for many pancreatic disorders including Recurrent Acute Pancreatitis (RAP), Idiopathic Chronic Pancreatitis (ICP), and recurrent “pancreatic-type” abdominal pain or in fact PD is an innocent bystander in a patient with ICP, who can present early as RAP, followed by pancreatic-type abdominal pain, and finally can present as a full-blown ICP [1]. Therefore, readers should have balanced views on this issue and appraise them carefully without (or the least) bias. In fact, the natural history of PD is difficult to follow since the diagnosis of PD is usually made after identifying the patients with pancreatic symptoms whereas asymptomatic PD patients are occasionally identified by incidental discovery from the radiographic images.

### What is PD?

PD is the most common congenital anomaly of the pancreas that the ventral (Wirsung) duct fails to fuse or fails to connect with the dorsal (Santorini) duct (complete PD) or the two ducts connect together via small side branches (incomplete PD). As a result, pancreatic drainage from pancreatic body and tail goes through the relatively small minor papilla. Thus, it has been proposed that the relative or functional outflow obstruction of the dorsal pancreas may pose the dorsal pancreas to RAP, CP, and the more controversial condition i.e. pancreatic type pain. Because PD is found in 8% of normal population from many autopsy studies [1], most PD are likely the innocent rather than the culprit. In addition, it has been estimated that only 5% of PD will become symptomatic [2].

To address whether PD causes RAP, CP or pancreatic pain, some critical questions should be answered. First, is PD more common in patients with RAP, CP, and chronic abdominal pain than asymptomatic population? Second, since the proposed pathogenesis of RAP, CP, and pancreatic pain from PD is the relative obstruction of the dorsal duct at the minor papilla, there should be evidence of isolated dorsal pancreatitis with normal ventral pancreas. Third, is there any other explanation of RAP, CP, and pancreatic type pain in such patients? Finally, does the PD patient who presented with pancreatitis get improve after the treatment to facilitate the outflow of PD?

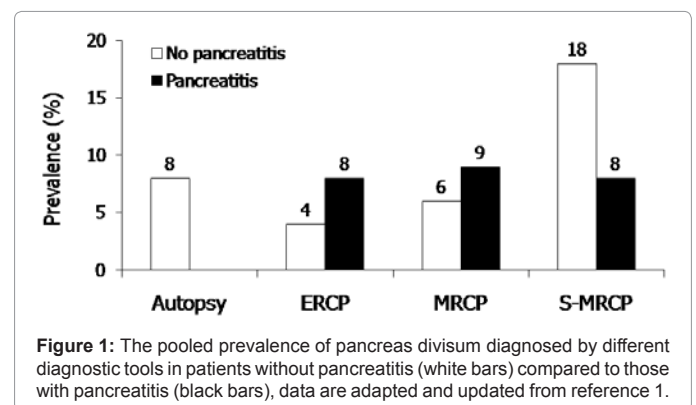
### Is PD More Common in RAP, CP, And Pancreatic Pain than General Population?

Before answering this question, we should know the accuracies of the various diagnostic tool of PD. The gold standard for the diagnosis of PD is still an autopsy. Data from a comprehensive review showed the autopsy prevalence of PD around 8% [1] but the prevalence in patients with pancreatitis is currently not available to compare.

Series on Endoscopic Retrograde Cholangiopancreatography (ERCP) studies demonstrated the prevalence of PD was around 8% in patients with pancreatitis compared to 3-4% in patients without pancreatitis [1,3]. These numbers are the main support for the belief that PD causes pancreatitis. However, the low (4%) ERCP prevalence

of PD in non-pancreatitis patients is a half lower than the number from autopsy studies [1]. This may either reflect the low sensitivity of ERCP for PD or the less effort of physicians to search for PD in patients without pancreatitis. In contrast, the higher prevalence of PD in patients with pancreatitis (8%) who underwent ERCP may be attributed from many reasons. Moreover, data mostly came from expert centers in pancreatic endotherapy, thus PD may be more dedicatedly sought. Another possible reason might be the referral bias (most patients with RAP who failed ventral duct cannulation, who possibly had PD, might be referred to these centers).

With the availability of Magnetic Resonance Cholangiopancreatography (MRCP) and, the more sensitive, secretin-enhanced MRCP, we now realize that the prevalence of PD in patients without pancreatitis is not lower than the prevalence of PD in patients with pancreatitis from ERCP series [1,3]. A recent comprehensive review [1] combined with a recent large population study from Japan [4] in PD patients without pancreatitis showed a higher prevalence of PD diagnosed by MRCP than that of from previous ERCP studies in the same type of patients (6% vs. 3%) [1,3]. Interestingly, with secretin-MRCP, they reported the highest prevalence of PD (18%) in non-pancreatitis patients [4]. It may be concluded that the prevalence of PD in patients with pancreatitis are not convincingly higher than that of controls (Figure 1). Needless to say, this recent evidence [4] does not support the hypothesis that PD as a cause of pancreatitis. In the authors' opinion, to avoid a more invasive diagnostic ERCP, secretin-MRCP may be a preferred option to screen for PD suspicions.

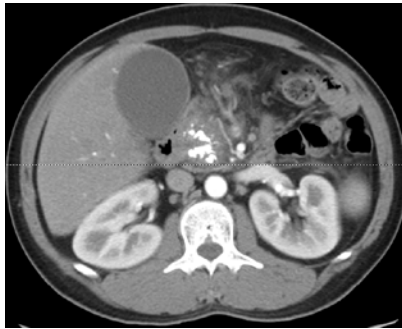


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**Figure 2:** A CT scan from a patient with idiopathic CP demonstrates pancreatic calcifications in both ventral and dorsal ducts. PD is unlikely to be the cause of CP in this patient.

### Is There Evidence of Isolated Dorsal Pancreatitis or Dorsal Duct Obstruction in Patients with PD and RAP, ICP, Or Pancreatic Pain?

Isolated dorsal pancreatitis is probably the most important evidence that PD in such patient is the causal etiology. Unfortunately, this information in most published studies on PD is usually lacking. However, there has been a reported case of PD with a pathologic isolated CP in dorsal pancreas with a completely normal ventral pancreas [5]. A recent comprehensive review demonstrated the presence of isolated dorsal pancreatitis varied from 25-88% of patients with PD and pancreatitis [1,6]. Thus, it may be undeniable that PD could cause disease in some patients. On the other hand, study of patients with PD and CP, of which most CP involved both dorsal and ventral pancreas (thus, PD was unlikely pathologic) showed that the natural course of CP with PD was similar to other usual causes of CP [6]. Thus, it is very critical to examine the evidence of pancreatitis (both parenchyma and duct) in the ventral pancreas before assuming the PD as a culprit of pancreatitis. Once ventral pancreas is heavily involved by pancreatitis, the possibility of PD as the cause of CP is unlikely (Figure 2).

### Is there any other Explanation of RAP, CP, and Pancreatic Pain in Patients with Pd?

There has been a growing body of evidence that proportions of patients with PD and RAP or CP has cystic fibrosis transmembrane conductance regulator (CFTR) mutations (22%) [7] and serine protease Kazal type 1 (SPINK1) mutations (42%) [8]. These frequencies were similar to the patients with RAP without PD [7,8] but higher than in patients with PD without pancreatitis (0%) [7]. We may interpret this information in 2 ways. First, PD may not be the cause of RAP or CP at all, but the real culprit is these genetic abnormalities. Evidence supported this hypothesis is that that patients with CP and PD had a natural course similar to patients with other CP [6]. Second, PD will cause diseases only in the presence of genetic susceptibility. This hypothesis is more attractive because at least one study has shown that the prevalence of PD (by MRCP) is very high (47%) in patients with CFTR-related pancreatitis compared to only 5% in patients with idiopathic pancreatitis without genetic mutations [9]. Thus, a combination of genetic susceptibility and pancreatic anatomical defect liked PD may explain why only certain PD patients developed pancreatitis.

### Do Patients with PD and Pancreatitis Improve after the Establishment of PD Drainage?

There are plenty of reported case series on endoscopic treatment and surgery on PD. Recent systematic review of these case series showed that the efficacy of endoscopic treatment of PD with RAP, CP and pancreatic pain were 79%, 69% and 54%, respectively [3] and the corresponding numbers for surgery were 83%, 67% and 52%, respectively [3]. However, it is difficult to conclude whether these treatments are better than placebo or sham procedure. Patients with RAP may stop having further attacks if the actual (unidentified) causes other than PD is unintentionally eliminated (e.g. drugs). For the symptom of pain, the placebo effect also cannot be ignored. For example, a recent meta-analysis reported the placebo response rate of 20% in CP patients with pain [10]. However, many original studies were retrospective series. Thus, a better Randomized Controlled Trial (RCT) is required to answer this question. So far, there has been only one RCT on endoscopic minor papillotomy in PD and RAP, which showed the better efficacy of endoscopic therapy than that of controls [11]. However, this study was rather small (9 and 10 patients in each arm), the follow-up time was also short (2.5 years) and patients were not blinded to the interventions. Therefore, it may conclude that there is a beneficial trend from the treatment of PD for RAP but larger studies to make stronger support is required.

### Conclusion: Which PD Patients should be Treated?

With the limitation of the current knowledge, the risks of the available treatments for PD (endoscopy and surgery), and the unconvinced efficacy of the treatments, a routine PD treatment for all pancreatic symptoms is not justified. In the authors' opinion, suitable candidates for the treatment of PD are probably; RAP without evidence of CP, isolated dorsal pancreatitis (either by CT, MRI, pancreatogram or EUS), pancreatic type pain with dilated dorsal duct or with Santorinicele [12], CP with genetic abnormality i.e. CFTR or SPINK1 mutations. On the other hand, PD patients with CP probably respond to PD drainage similar to CP patients from other etiologies. Among all PD patients who deem for PD treatment, PD patients with only pancreatic type pain are the vaguest patients with the poorest response.

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