

Opie's hypothesis revisited: Acute pancreatitis due to bile reflux into the pancreas

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More than 100 years ago, Ernest Opie suggested that a common channel between the pancreatic duct and the common bile duct is created when a gallstone becomes impacted at the duodenal papilla. He proposed that bile would regurgitate into the pancreas and thus trigger pancreatitis [1]. This has become a cornerstone of the proposed pathogenesis of biliary pancreatitis. However, despite the experimental proof of duct ligation and retrograde injection of bile or bile salts, clinical proof of this hypothesis, especially in patients not suffering from gallstones, has been sparse. Further, this 'common channel theory' has been questioned because the secretory pressure in the pancreatic duct exceeds the pressure in the bile duct [2]. Moreover, perfusion of bile through the pancreatic duct at physiological pressure does not result in pancreatitis and the pancreatic duct remains unharmed [3,4]. We here report the case of a 40-year old male with repetitive episodes of pancreatitis for four years when he was 34 years old who had in total 10 episodes of acute pancreatitis.

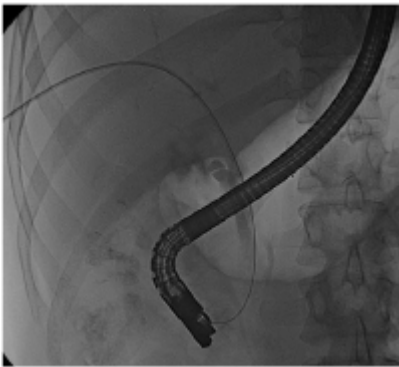
The patient was a non-smoker and never drunk alcohol. Carbohydrate deficient transferrin (CDT) was normal on several occasions. With both transabdominal and endoscopic ultrasound, neither overt gallstone nor sludge/microlithiasis were detectable on several occasions in conjunction with episodes of pancreatitis or during the interval. The patient did not suffer from overt diabetes mellitus and HbA1c was normal. Analysis for known genes altered in pancreatitis did not reveal any mutation in PRSS1, SPINK1, CTFR, and CFTR [5]. Cross-sectional imaging (MDCT and MRI/MRCP) demonstrated acute pancreatitis without any signs of chronic pancreatitis. Anatomic abnormalities (pancreas divisum or other branching abnormalities) could not be detected. Several attempts to cannulate either the bile duct or the pancreas duct during endoscopic retrograde cholangiopancreatography (ERCP) at three centers were unsuccessful. Upon endoscopy, the papilla appeared completely normal. After extensive discussions with the patient and written informed consent, we eventually agreed to perform a PTC-guided rendezvous ERCP.

Percutaneous transhepatic cholangiography (PTC) demonstrated normal intrahepatic bile ducts. When further contrast medium was slowly and carefully injected, the contrast first filled the pancreatic duct before passing through the papilla major (Fig. 1). A long guidewire was advanced through the papilla, taken up by a forceps, and the sphincterotome was introduced over the wire. A biliary sphincterotomy was executed

without complications. Further visualization of the MPD did not show evidence of chronic pancreatitis. After this endoscopic procedure, the patient was without symptoms and never experienced another episode of acute pancreatitis during a seven-year follow-up.



A



B

Fig. 1. A. Fluoroscopy of initial filling of the bile ducts during PTC. Note the reflux into the main pancreatic duct (arrow). B. Fluoroscopy after introducing the guidewire prior to sphincterotomy: the contrast medium completely emptied from both the bile and pancreatic duct.

Since its original proposal, the hypothesis of Opie [1], which he proposed for gall stone pancreatitis, is a cornerstone in pancreatic pathophysiology, and in the concept of how acute biliary pancreatitis does develop. In the past, there has been some case reports proving the common channel theory in conjunction with gallstones [2], however, the pathomechanism could be just opposite to what was proposed initially. In another case report involving a patient with a pancreatobiliary maljunction, orthograde flow of bile through the pancreatic head did not cause any pancreatitis [6]. An interesting

mechanism involving at least two gallstones and a toxic bile-pancreatic juice mixture accessing the pancreas has been proposed based on some animal experiments [7], however, without clinical evidence [8].

The PTC performed in this patient proved that biliopancreatic reflux occurred and that by opening of the papilla the attacks of acute pancreatitis completely vanished. The cannulation of the papilla was impossible but also not forced by aggressive precut strategies. ERCP with sphincterotomy demonstrated nothing particular about this papilla. Nevertheless, the reason for the relative papillary obstruction causing the reflux into the pancreatic duct prior to outflow in the duodenum remains obscure. One explanation, though, could be a papillitis, which in turn caused the congestion. This mechanism has been proposed for patients with diabetes mellitus and chronic pancreatitis [9]. However, we did not recognize any signs of papillitis or papillary stricture upon ERCP and the patient did not have diabetes mellitus. Another possibility would be a so-called long channel, i.e. a joint papillary duct segment of >6 mm, which is associated with a higher rate of pancreatitis [10] but not with papillary stenosis or inability to cannulate. Such a long common channel, indeed, can be suggested from Opie's original work [1] and is present in our patient. Demonstration of the direct biliary reflux adds a piece to the puzzle of the pathogenesis in acute pancreatitis, proving one point of Opie's original hypothesis [1].