PICTORIAL ESSAY Abdominal imaging

Embryological Development and Congenital Anomalies of the Pancreas: A Pictorial review

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ABSTRACT

This review highlights the characteristics in Imaging of congenital anomalies and variants of normal anatomy of the pancreas by providing an overview of the most common among them. Important embryologic events are noted to emphasize the mechanisms of their formation. The radiologic appearance at different modalities is presented, focusing mainly on computed tomography, magnetic resonance imaging, endoscopic retrograde cholangiopancreatography, and MR cholangiopancreatography. The purpose of this essay is to familiarize clinicians and radiologists with these appearances and help prevent misdiagnosis in everyday practice.

KEY WORDS
Pancreatic embryology; developmental anomalies; annular pancreas; pancreas divisum; circumportal; ansa pancreatica; crocodile jaw sign; crossing duct sign;

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Introduction

As abnormal radiological findings concerning the pancreatic gland are not that infrequently encountered, understanding normal and deviant developmental processes is crucial in identifying these anomalies at diagnostic imaging. This article aims to 1. familiarize radiologists with key aspects of pancreatic anatomy and physiology; 2. stress out developmental interactions that affect pancreatic development; 3. provide a compact description of congenital anomalies (pancreas divisum, annular and circumportal pancreas, pancreatic agenesis and hypoplasia, ectopic pancreas and congenital cysts) and variants of normal pancreatic configuration (ductal variants and ansa pancreatica, anomalous pancreaticobiliary junction) that constitute some of the expected atypical findings.

Elements of pancreatic anatomy and physiology

The pancreas is a gland with coarse lobulated morphology, situated within the anterior pararenal retroperitoneal space.[1] Anatomically it is divided into the head, engulfed in the descending part of the duodenum, the neck, the body, the tail, and the uncinate process. The tail, the distal part of the organ, lies in the hilum of the spleen inside the peritoneal cavity (Fig. 1).[2] Derived from the foregut, the pancreas has endodermal origins and undergoes nuanced differentiation to become an organ with both exocrine and endocrine functions.[2] The function of the exocrine pancreas is the production and secretion of an alkaline solution of proteolytic, lipolytic, and amylolytic enzymes. This solution, the pancreatic chyme, helps adjust luminal ph to the level that gives the optimal activity of pancreatic enzymes.[3] Vagal discharge, cholecystokinin, and secretin stimulate the release of pancreatic enzymes from the acinar cells of the gland, where they have been synthesized and stored as inactive precursors. Secretion of the pancreatic chyme is facilitated by a network of small ducts that join to form the main and the accessory pancreatic duct (Fig. 2).[2],[3] The main duct or duct of Wirsung courses the gland from the tail to the head where it unites with the common bile duct (CBD) and drains together into the duodenal lumen through the major duodenal papilla or ampulla of Vater.[3] To enter the duodenum, the distal CBD and the duct of Wirsung transverse the sphincter of Oddi, which consists of three separate smooth muscles. In most cases, (80-90%) the ducts unite within this sphincteric segment. The shorter accessory duct or duct of Santorini drains a part of the pancreatic head and enters the duodenum 2-2.5cm proximal to the ampulla of Vater, at the minor duodenal papilla.[4] In 30% of individuals, the duct of Santorini loses its communication with the minor papilla and persists only as a branch of the main pancreatic duct.[4]

The endocrine pancreas is organized in functional units dispersed throughout the gland, the islets of Langerhans, that consist of discrete types of cells. From the islets of Langerhans, a host of hormones are secreted directly into the circulation: α-cells: glucagon; β-cells: insulin; δ-cells: somatostatin; ε-cells: ghrelin; γ [or PP]-cells: pancreatic polypeptide.[2],[5]

The pancreas receives a double arterial supply from branches of both the celiac trunk (superior pancreaticoduodenal artery) and superior mesenteric artery (inferior pancreaticoduodenal artery) that join to form an arcade. Tributaries from the splenic artery supply the body and tail. Venous drainage typically follows the arterial supply and drains into the portal venous system.[2],[3]

Embryology of the pancreas and biliary tree

Early in the fourth week of embryological development, a hepatic diverticulum appears in the ventral wall at the junction of the primitive foregut and midgut. This small diverticulum is the anlage for the development of the liver, extrahepatic biliary ducts, and gallbladder (Fig. 3).[6] At the end of the fourth week, two buds are recognizable in the hepatic diverticulum: the cranial one becomes the liver and the extrahepatic biliary tree; the caudal one will further divide into superior and inferior. The gallbladder and cystic duct appear from the superior bud, while from the inferior develop the right and left ventral pancreas.[6]

By the fifth embryonic week, two endodermal buds give rise to primitive pancreatic tissue. The right and left ventral bud will become the pancreatic head and uncinate process. From the larger dorsal bud, the neck, body, and tail of the pancreas will form.[2],[7] Approximately at gestational day 33, a microscopic luminal network forms in the dorsal bud that become the ductal system responsible for handling exocrine secretions. Even though most of the pancreas forms from the dorsal anlage, its associated duct becomes the accessory

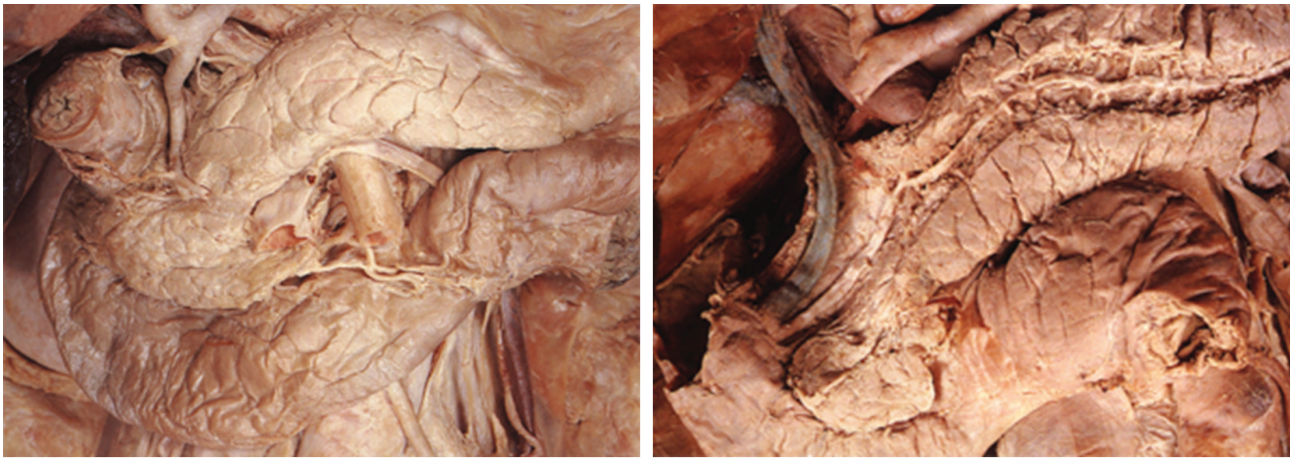

Fig.1. (Left) *Cadaveric anatomy of the human pancreas, and adjacent structures.* ***(Right)*** *The pancreatic ductal system. The main pancreatic duct is seen entering the duodenal wall together with the common bile duct at the level of the major duodenal papilla.*

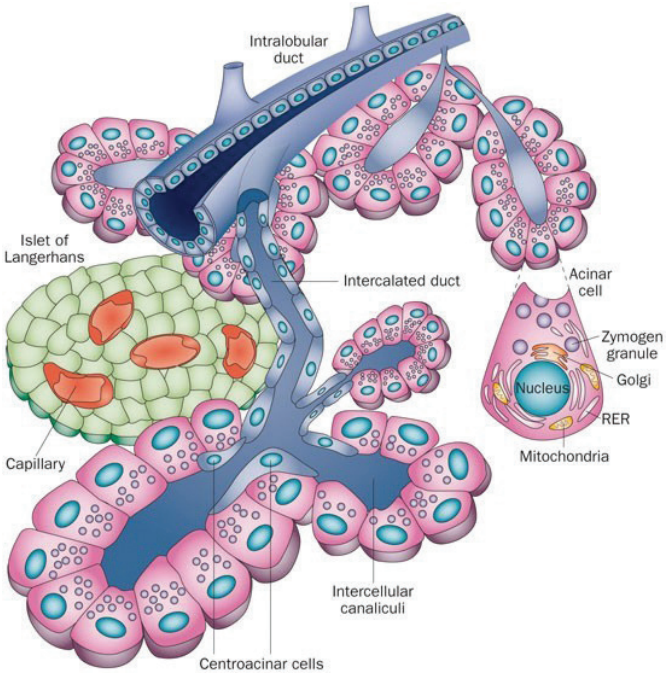

Fig. 2. *The components of the pancreas. The pancreas consists of endocrine cells localized within structures named the Islets of Langerhans, which contain multiple endocrine cell types and the exocrine pancreas, which is composed of acinar calls and ductal structures. Pancreatic acinar cells form a basic structure called an acinus that surrounds a central lumen open to the duct system. Pancreatic acinar cells produce, store and secrete enzymes necessary for the digestion and absorption of food in the small intestine. Digestive enzymes are secreted through the apical membrane of the acinar cell into small, intercalated ducts that are directly connected to increasingly larger intralobular ducts that join the main pancreatic duct. The main pancreatic duct joins the common bile duct just prior to the ampulla of Vater, where both pancreatic and liver products enter the small intestine. Blockage of the passage of materials through the ampulla of Vater leads to increased pressure in the duct system and gives rise to pancreatic inflammation. [Logsdon et al., The role of protein synthesis and digestive enzymes in acinar cell injury]*

duct of Santorini. Conversely, the main pancreatic duct originates from the smaller ventral anlage.[2]

During the sixth week, the dorsal pancreas elongates and enters the dorsal mesentery: from this embryological process stems the intraperitoneal position of the pancreatic tail. As the foregut tube grows, developmental forces pull the ventral pancreatic diverticulum and the common bile duct counterclockwise around the primitive duodenum and reposition them into a dorsal position.[2] This allows for the fusion of the ventral and dorsal pancreatic buds at approximately gestational day 37.[8] The entrance of the common bile duct into the left posterior surface of the duodenum can be seen.[6]

In the seventh intrauterine week, the ducts from the two pancreatic buds fuse. Preferably, after birth, pancreatic secretions flow through the main pancreatic duct as the portion of the accessory duct distal to its un-

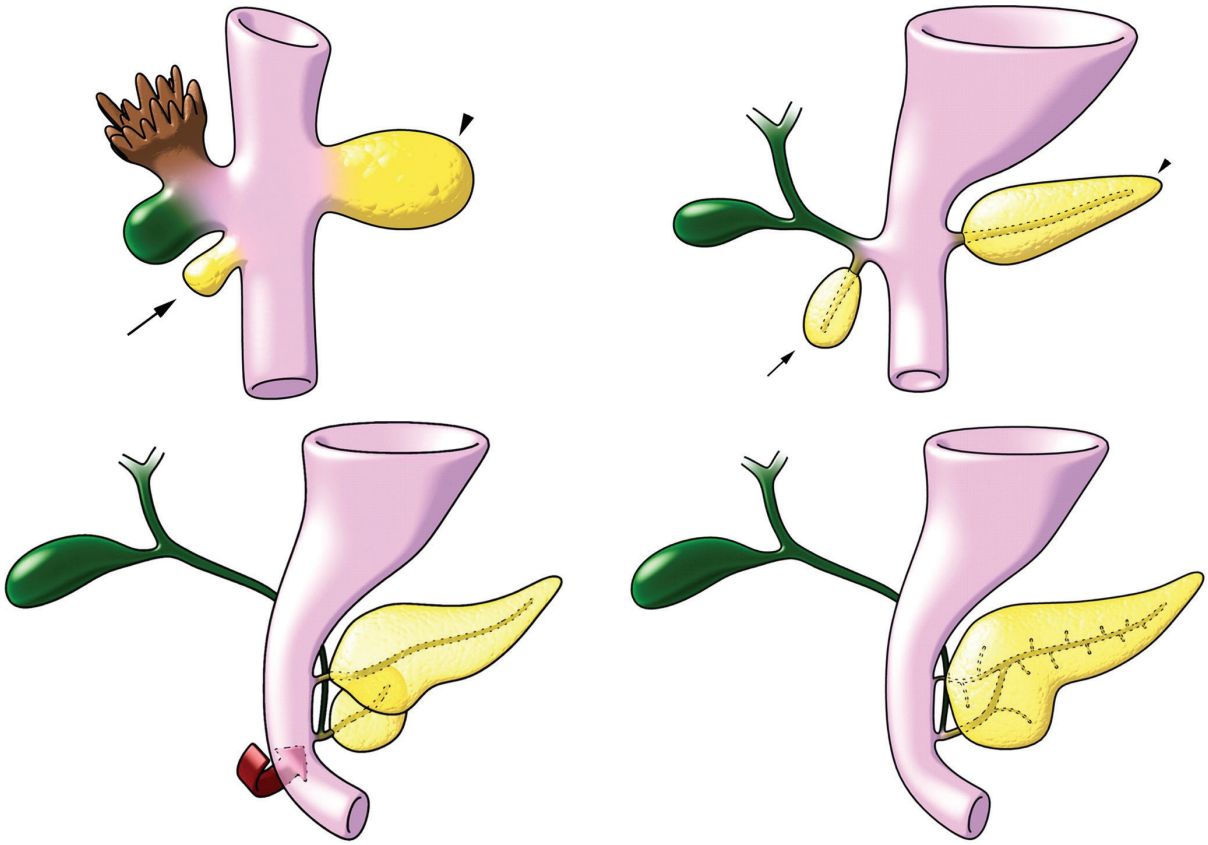

Fig. 3. *Illustration of the embryological processes of pancreatic development. [Mortelé, K.J., Multimodality Imaging of Pancreatic and Biliary Congenital Anomalies]*

ion with the main duct obliterates or becomes stenotic in most individuals.[2] At the same time, the bile and pancreatic ducts end in close cavities in the duodenal wall and further elongation pushes the pancreaticobiliary junction out, to the level at which the intestinal muscle is forming.[6]

In the eighth week, the site of the junction comes to lie within the submucosal layer of the duodenal wall, and around the tenth week, the muscles of the sphincter of Oddi undergo differentiation.[6]

Developmental interactions that affect pancreatic embryology

Interactions between developing endodermal structures dictate further differentiation and tissue specification. The common origin of the ventral pancreas with the liver and the biliary tree demands the presence of mediating signals that define organ fate (Fig. 4). It has been shown that the ventral endoderm gives rise to liv-

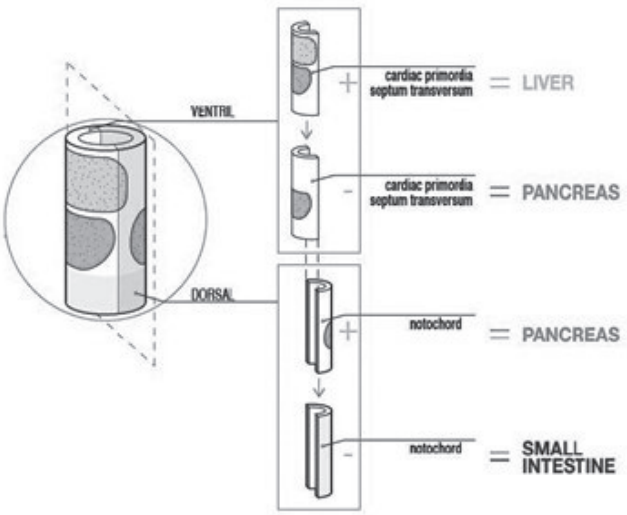

Fig.4. *Schematic representation of interactions defining default patterns for pancreatic development. [Pin C and Fenech M, (2017), Development of the Pancreas, Pancreapedia: Exocrine Pancreas Knowledge Base]*

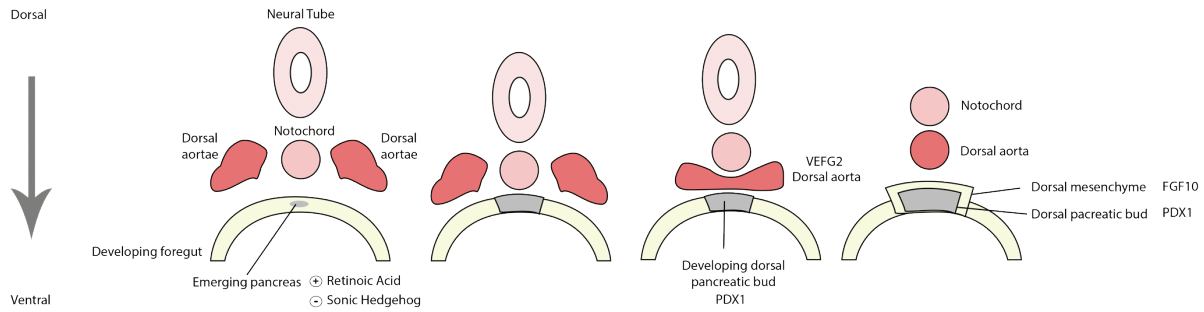

Fig.5. *Specification of the dorsal pancreatic bud and interactions with the developing vasculature and mesenchyme. Interactions with the dorsal mesenchyme but primarily with the notochord lead to inhibition of Sonic Hedgehog (SHH) expression in the foregut endoderm and progression to a pancreatic fate. The foregut expresses SHH along its length except at the point of proximity with the notochord. Pancreatic and duodenal homeobox gene 1 (PDX1 or formerly known as Insulin Promoting Factor 1), and its interaction with Vascular Endothelial Growth Factors (VEGFs) expressed by the adjacent vascular structures, is required for expansion and subsequent differentiation of the pancreas. [Pin C and Fenech M, (2017), Development of the Pancreas, Pancreapedia: Exocrine Pancreas Knowledge Base & Mühlemann M., THES, (2018), Intestinal stem cells and the Na+-D-Glucose Transporter SGLT1: potential targets regarding future therapeutic strategies for diabetes.]*

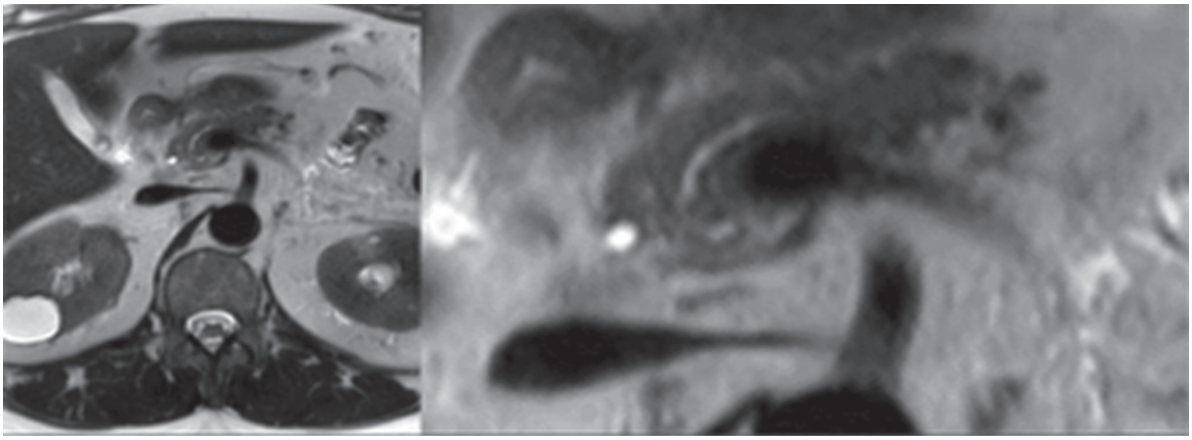

Fig.6. *MRI. Partial dorsal agenesis of the pancreas.*

er tissue in the presence of inhibitory signals from the septum transversum and cardiac primordia, while the absence of this signals result in pancreatic differentiation suggesting that the default pattern of differentiation is pancreatic tissue. Similarly, for the dorsal endoderm, inductive signals from the notochord and dorsal mesenchyme promote dorsal pancreatic development, and the absence of those, defines non-pancreatic differentiation, namely to small intestine. [9]

Paracrine signaling from the developing vasculature is also crucial for pancreatic formation and specification, particularly for the dorsal pancreatic bud.[9] Direct interactions with endothelial cells as well as interactions via circulating signals induce bud formation and balance endocrine and exocrine differentiation (Fig. 5).[9] The term angiocrine has been proposed to indicate the capacity of endothelial cells to release growth factors and cytokines that may be involved in organogenesis.[10],[12]

DEVELOPMENTAL ANOMALIES OF THE PANCREAS

Pancreatic Agenesis and Hypoplasia

The spectrum of complete or partial absence of the pan-

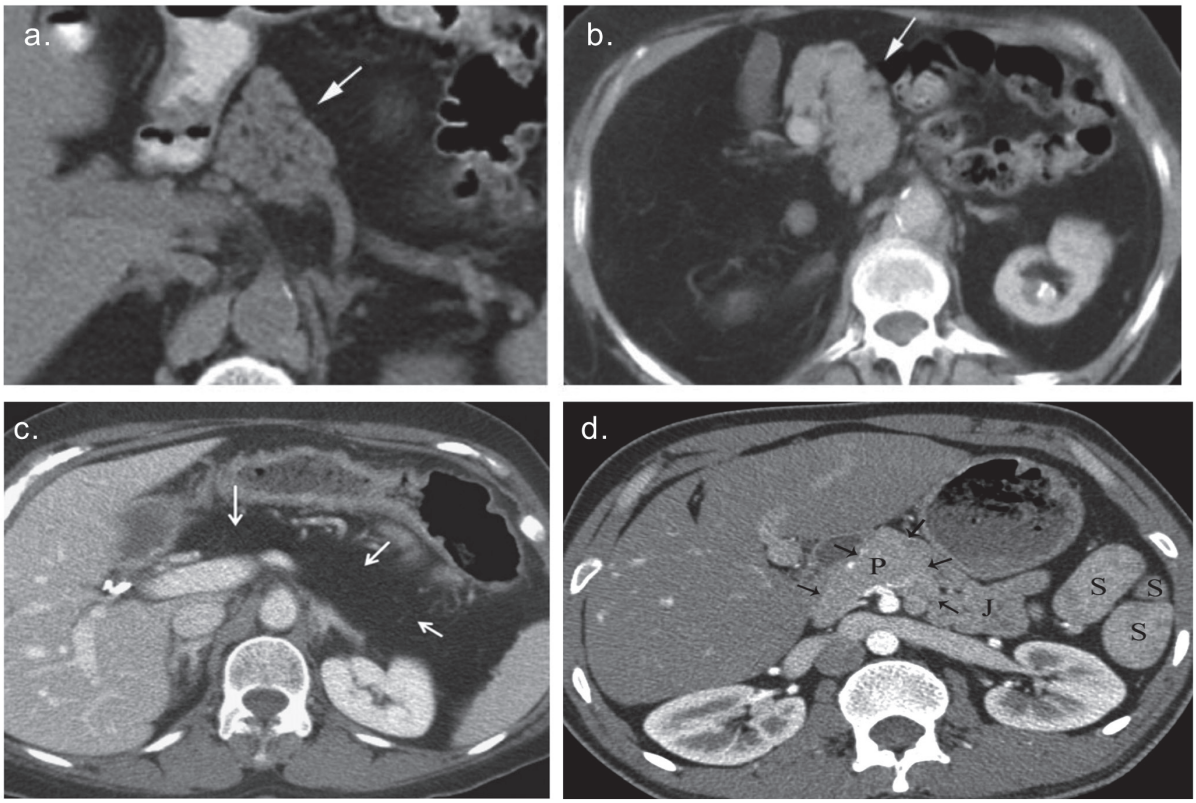

Fig.7. *Pancreatic hypoplasia, CT scans.* ***a.*** *Absence of the pancreatic neck, body and tail with presence only of the pancreatic head (arrow).* ***b.*** *A truncated midline pancreas in a patient with heterotaxy syndrome. [Mortelé, K.J., Multimodality Imaging of Pancreatic and Biliary Congenital Anomalies]* ***c.*** *Fatty infiltration of the pancreatic body and tail. [Alexander L. Congenital Pancreatic Anomalies, Variants and Conditions]* ***d.*** *Partial dorsal agenesis of pancreas (arrows) in patient with polysplenia syndrome; small bowel loops seen in the dorsal pancreatic bed. P: pancreas, J: jejunum, S: spleen. [Türkvatan A., Congenital Variants and Anomalies of the Pancreas and Pancreatic Duct]*

creatic gland is an entity associated with genetic abnormalities (Fig. 6).[2] Aplasia of the pancreas is extremely rare and incompatible with life.[4] Agenesis and hypoplasia occur in the setting of various syndromes presenting as exocrine insufficiency, permanent neonatal diabetes mellitus, and pancreatitis starting in utero or early in neonatal life.[2] The first gene identified for which an inactivating mutation caused dorsal agenesis of the pancreas was PDX1, which defines the earliest pancreatic endoderm and is expressed in the emergent buds. Pancreas-specific transcription factor 1a (PTF1A) has a fundamental role in early pancreas specification from foregut endoderm and associated mutations result in pancreatic agenesis with or without cerebellar agenesis. GATA family transcription factors regulate proliferation and differentiation in a number of endodermal organs.[5] Mutations in GATA-binding protein 6 (GATA6) are now believed to be the most common cause of pancreatic agenesis and hypoplasia with associated structural cardiac defects and other less frequent gastrointestinal abnormalities.[2],[5] Pancreatic hypoplasia is observed in Johanson-Blizzard syndrome, an autosomal recessive disorder caused by an inactivating mutation in UBR1 (E3 ubiquitin ligase). Ubiquitin ligase is crucial for the degradation of aged intracellular proteins and mutations reducing enzymatic function cause toxic accumulation of aged proteins. Acinar cells in the pancreas require some of the highest ubiquitin levels to maintain normal exocrine function. Hypoplasia and exocrine insufficiency are also present in Alagille syndrome, an autosomal dominant disorder caused by defective NOTCH signaling, in which biliary abnormalities

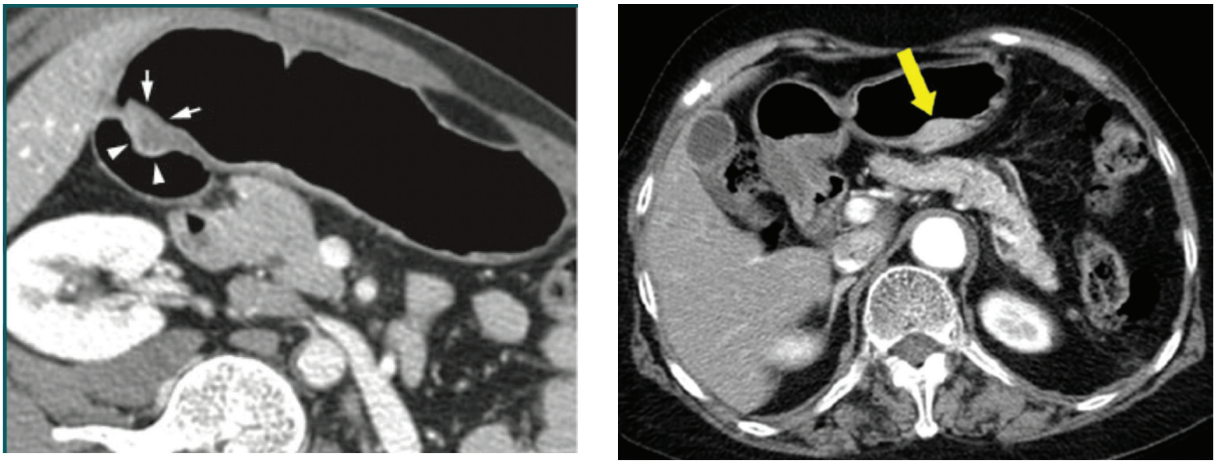

Fig.8. (Left) *Ectopic pancreas at gastric antrum. CECT shows an ill-defined flat-ovoid 1.4-cm endoluminal submucosal mass (arrows) in the anterior wall of the gastric prepyloric antrum. The lesion shows heterogeneous enhancement and low attenuation. Note the prominent enhancement and mild thickening of the overlying mucosal layer (arrowheads). [Kim J., Ectopic Pancreas: CT Findings with Emphasis on Differentiation from Small Gastrointestinal Stromal Tumor and Leiomyoma.]* ***(Right)*** *Heterotopic pancreas in stomach. CT image shows an enhancing mass (arrow) in gastric antrum. The mass reveals ill-defined border and endophytic growth. [Kim S., Various congenital abnormalities and anatomic variants of the pancreas: A pictorial review]*

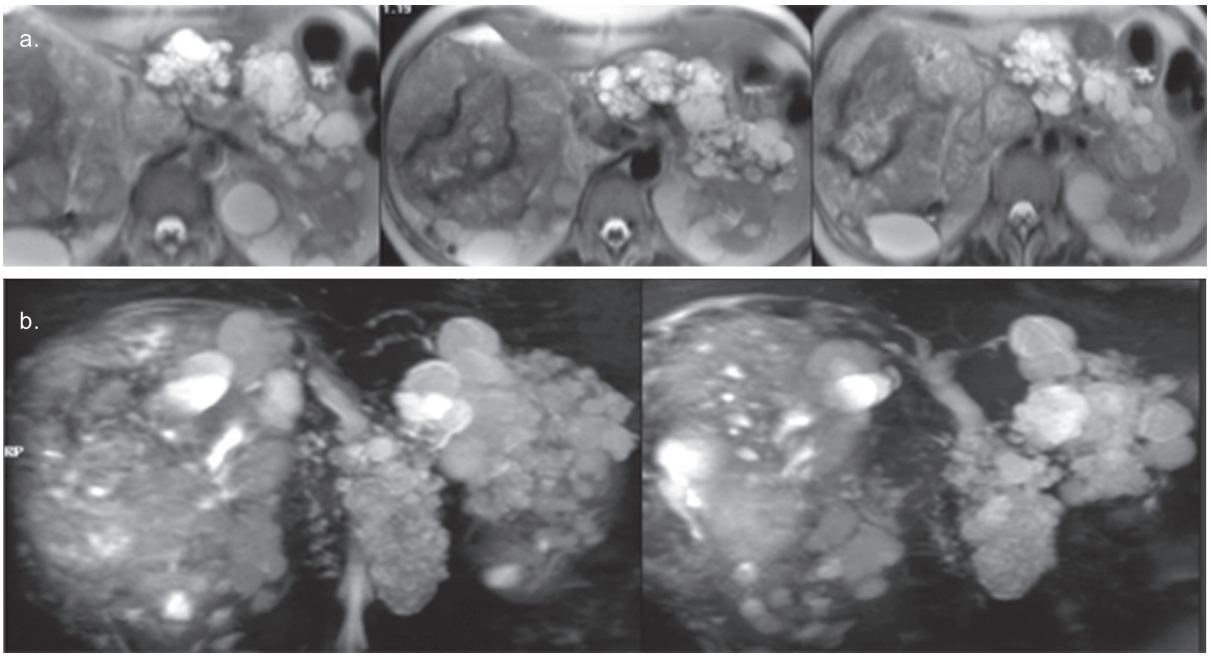

Fig.9. (a), (b) *MRI. Multiple pancreatic cysts.*

predominate. Campomelic dysplasia, a skeletal disorder caused by haploinsufficiency of SOX9 (an effector of NOTCH signaling) leads to death soon after birth, disorders of sex differentiation (i.e. 46, XY), and hypoplasia of the entire pancreas.[2],[5] Ivemark syndrome, a rare sporadic or autosomal recessive heterotaxy syndrome, presents as cystic dysplasia of the pancreas, liver, and kidneys, asplenia or hypoplasia of the spleen, complex cardiac malformations, and intestinal malrotation amongst others.[2],[5]

At imaging, complete dorsal pancreatic agenesis presents as the absence of the neck, body, and tail of the

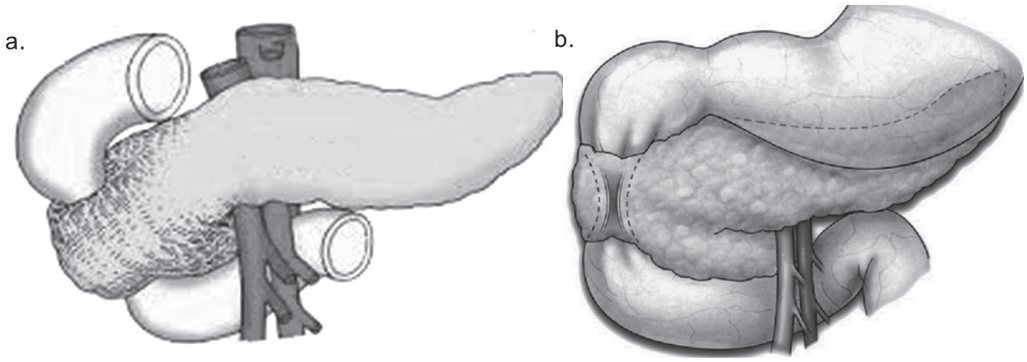

Fig.10. (a, b.) *Illustration of an annular pancreas, demonstrating the existence of pancreatic tissue circumferentially placed around the duodenum, as a result of malrotation of the ventral pancreatic anlage.*

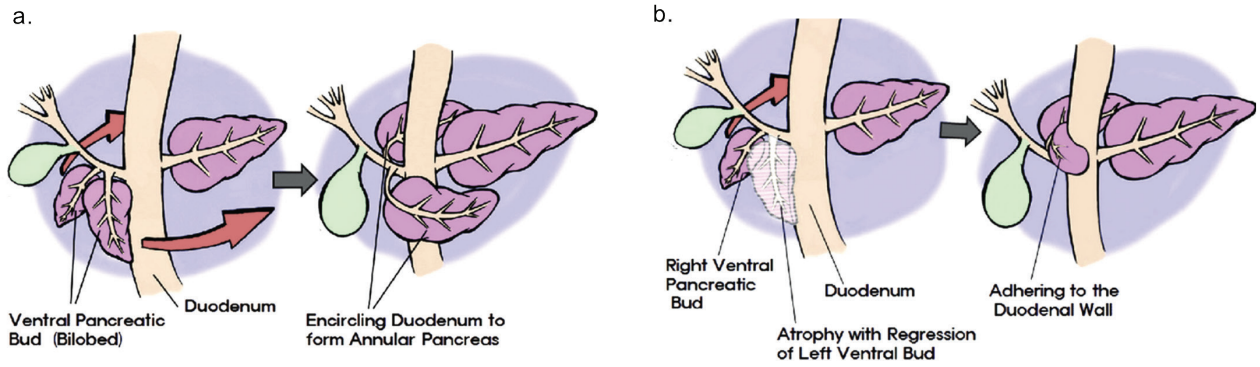

Fig.11. *Theories of annular pancreas development.* ***(a.)*** *Diagram illustrates Baldwin's theory of the development of annular pancreas, in which the left ventral bud persists and migrates around the duodenum in opposite directions to fuse with the dorsal pancreatic bud.* ***(b.)*** *Diagram illustrates Lecco's theory of the development of annular pancreas, in which the left ventral bud regresses and the right ventral bud adheres to the duodenal wall and becomes stretched and elongated with rotation. [Lee et al. Complications of Congenital and Developmental Abnormalities of the Gastrointestinal Tract in Adolescents and Adults: Evaluation with Multimodality Imaging.]*

pancreas as well as the absence of the duct of Santorini and minor duodenal papilla. Partial agenesis of the dorsal pancreas manifests as a variable size of the pancreatic body with a present remnant of the duct of Santorini. When there is suspicion of dorsal agenesis, pancreatic carcinoma with upstream atrophy of the gland must be ruled out. Fatty replacement of the distal pancreas can also be a mimic. The presence of the stomach or intestine in the pancreatic bed is an indicator of pancreatic agenesis (Fig.7).[1],[4],[8]

Heterotopic or Ectopic Pancreas

Ectopic pancreatic tissue is found in 0.6-13.7% of the population.[4] Defined as pancreatic tissue separated from the gland, the commonest ectopic sites are the stomach (up to 38% of cases), the duodenum (up to 36%), jejunum (16%), ileum or Meckel diverticulum.[8],[14] More rare sites include the colon, oesophagus, gallbladder, bile ducts, liver, spleen, umbilicus, mesentery, mesocolon, or omentum.[14] The ectopic pancreatic tissue usually measures <2cm in its largest dimension and in half of all cases it is located in the submucosa.[4] In some cases, a duct can also be present in the ectopic pancreatic tissue. The clinical significance lies in the complications that can arise as the ectopic pancreas is usually asymptomatic on its own: inflammation, stenosis, ulceration, intussusception, bleeding, and malignancy including adenocarcinoma and endocrine tumors.[4],[13]

The accepted theory for the embryological origin of this anomaly is remnants of cells of the primitive ven-

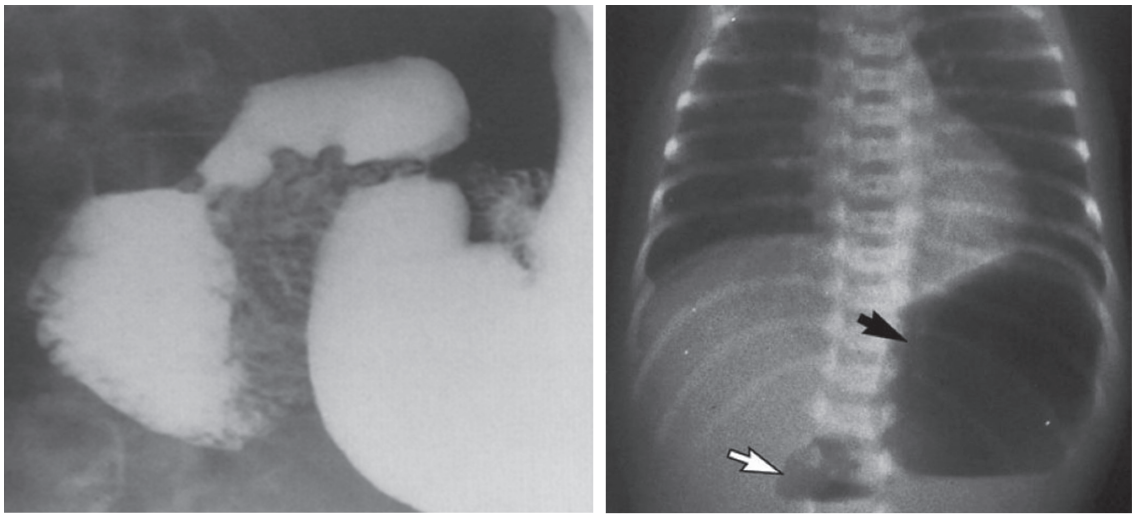

Fig.12. (Left) *Upper GI barium meal examination showing narrowing of the duodenal lumen caused by annular pancreatic tissue.* ***(Right)*** *Annular pancreas on plain abdominal film of a child presenting as "double bubble" sign: the larger proximal bubble is caused by gastric distention (black arrow) and the smaller distal by the dilated duodenal bulb (white arrow).*

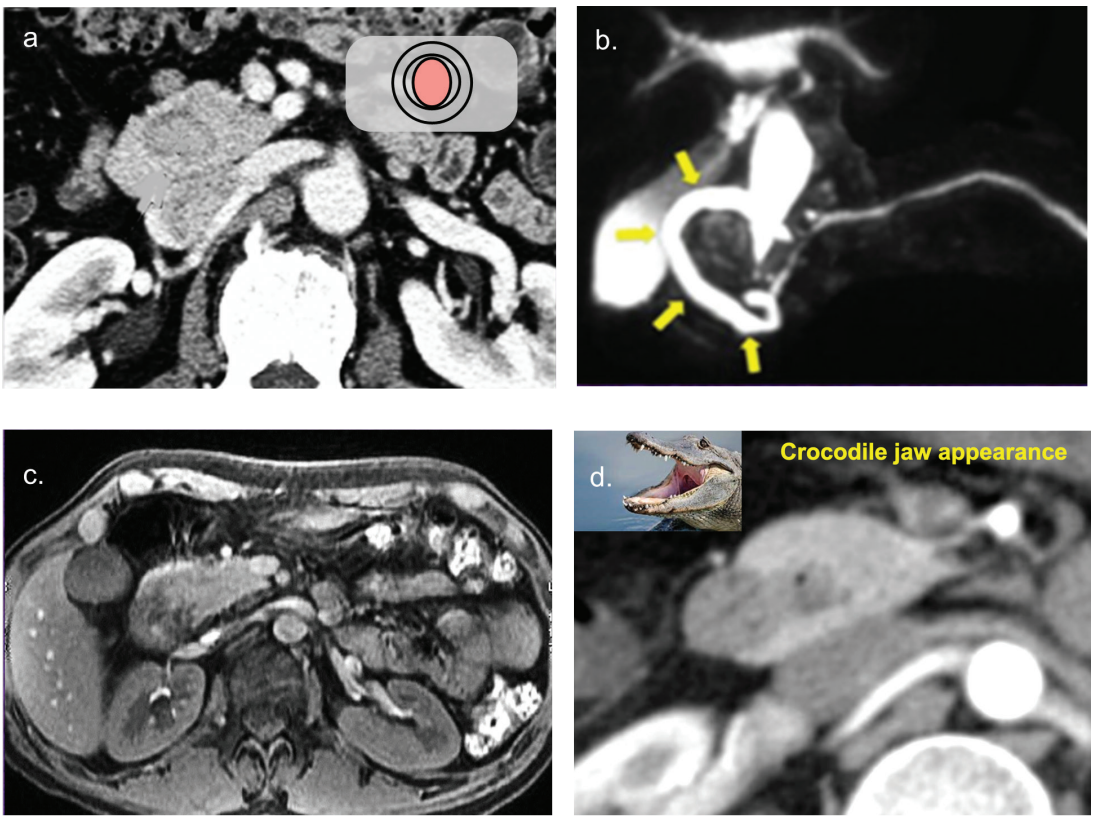

Fig. 13. (a.) *CECT. Complete type of annular pancreas. The pancreatic tissue encircles the duodenum.* ***(b.)*** *MRCP. Extramural type of annular pancreas. The yellow arrows indicate the annular duct in the extramural passing posteriorly and wrapping around the descending duodenum.* ***(c, d.)*** *MRI & CECT respectively. The "crocodile jaw appearance" is produced by an incomplete encasement of the duodenum by pancreatic tissue.*

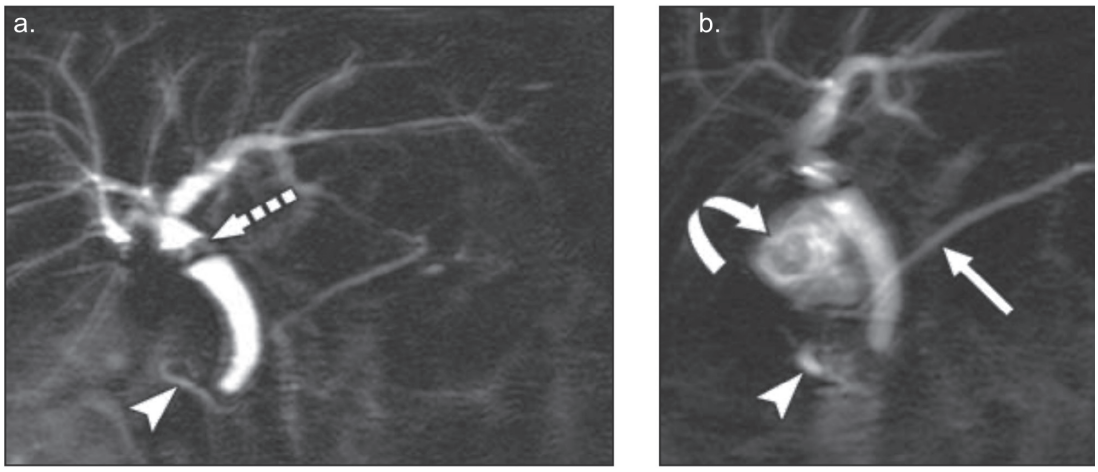

Fig. 14. *46-year-old woman with chronic pancreatitis.* ***a.*** *Pre-secretin MRCP image shows annular duct (arrowhead). Apparent filling defect at common hepatic duct (arrow) is caused by crossing vessel.* ***b.*** *MRCP image obtained 7 minutes after injection of secretin shows irregularity of annular duct with side branch dilatation (arrowhead). Chronic pancreatitis is predominantly confined to annulus, with main duct (straight arrow) exhibiting normal caliber without structure or side branch disease. Although it can be appreciated before secretin injection, pancreas divisum is better visualised on secretin-enhanced images. Use of secretin also allows functional assessment of pancreatic exocrine reserve. At expected peak of action, exocrine output fills only duodenal bulb (curved arrow), indicating suboptimal response. [Sandrasegaran et al., Annular Pancreas in Adults].*

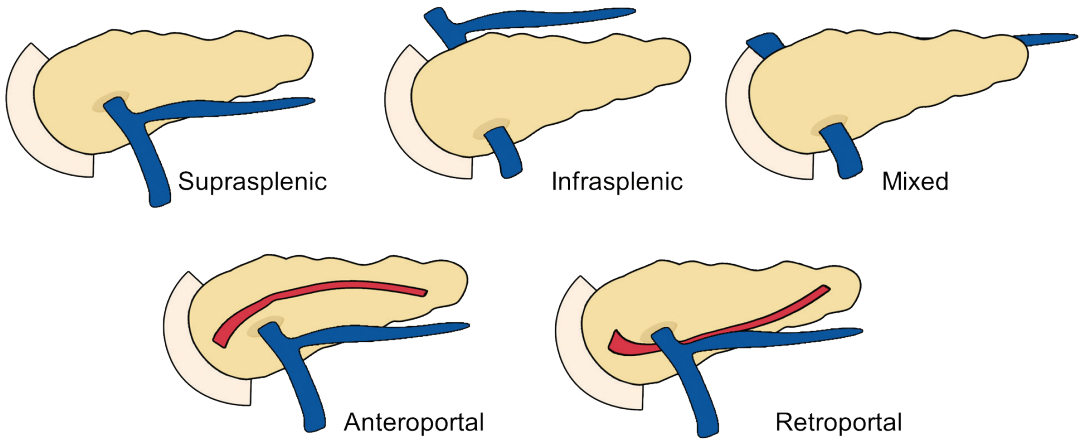

Fig. 15. *Circumportal pancreas morphology and classification*

tral and dorsal anlage in the GI tract that develop to form the heterotopic pancreas, associated with defective NOTCH signaling pathways and mutations in Neurog3 (neurogenin 3).[2] Although this lesion cannot be accurately differentiated -radiologically- from other submucosal tumors such as GISTs or leiomyoma, Kim et al. have reported some prominent CT findings in favor of ectopic pancreatic tissue: 1. Prepyloric antral or duodenal location, 2. Ill-defined border, 3. Flat shape, defined as a long diameter to short diameter ratio greater than 1.4, 4. Prominent enhancement of overlying mucosa and 5. Endoluminal growth pattern (Fig. 8).[15]

Cystic dystrophy of the ectopic tissue is a serious complication that affects most often the duodenal wall in the site of the minor papilla. It represents the remodeling of the pancreatic tissue as a result of repeated inflammation due to small duct obstruction. Chronic alcohol consumption is thought to trigger dystrophic

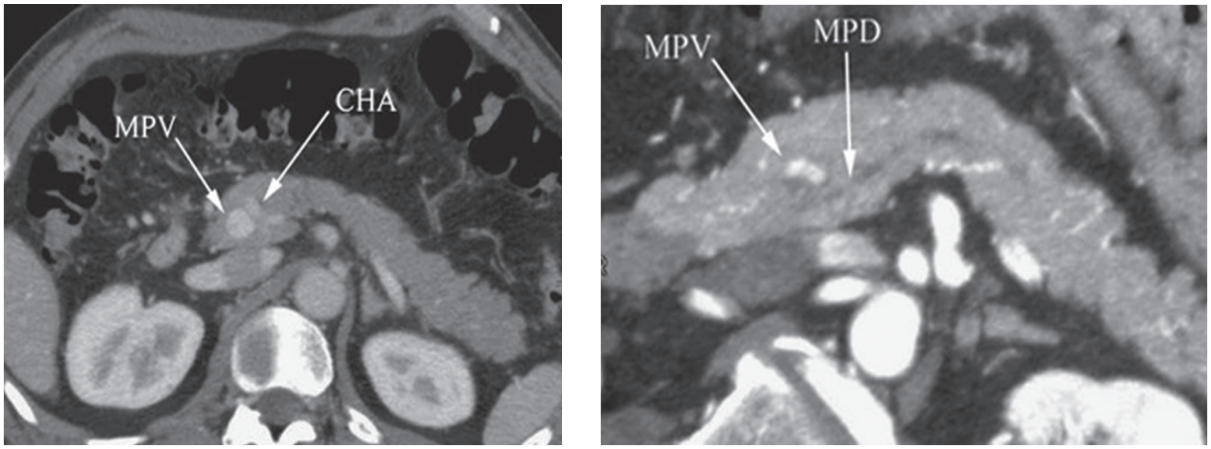

Fig.16. *Circumportal pancreas* ***(Left)*** *CECT. Encasement of the main portal vein and the common hepatic artery (CHA) by pancreatic parenchyma.* ***(Right)*** *Retroportal course of the main pancreatic duct (MPV). [Ishigami K., The prevalence of circumportal pancreas as shown by multidetector-row computed tomography].*

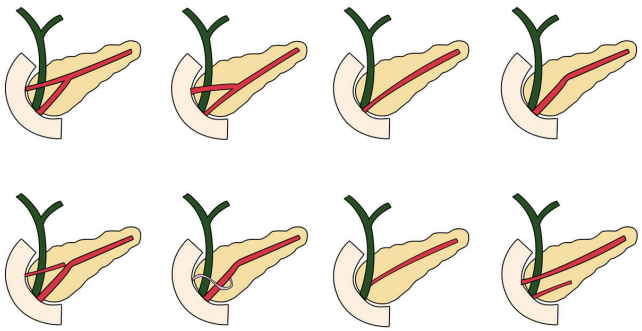

Fig.17. *From top left to bottom right:*
1.*Typical configuration;*
2. *Bifid configuration with dominant duct of Santorini;*
3. *Completely obliterated duct of Santorini;*
4. *Vertical duct of Wirsung;*
5. *Partial obliteration of the duct of Santorini at proximal point of junction;*
6. *Ansa pancreatica;*
7. *Anomalous pancreaticobiliary junction;*
8. *Pancreas divisum.*

Pancreatic ductal variants.

changes. Imaging findings include thickening of the duodenal wall with moderate to strong enhancement. The presence of small cysts in the thickened duodenum and inflammation of adjacent tissues with or without lymphadenopathy is also noted.[13]

Congenital Pancreatic Cysts

Congenital pancreatic cysts are a very rare entity, typically affecting children with varying clinical presentation from asymptomatic to a palpable abdominal mass, abdominal distention, and symptoms of compression of adjacent structures.[13] They develop from the primitive pancreatic ducts and are lined by cuboidal epithelium.[13] They are most commonly located in the body and tail and can be single or multiple.[4] Multiple pancreatic cysts are observed typically in association with systemic diseases, namely Von Hippel-Lindau, Beckwith-Wiedeman syndrome, and polycystic disease of the pancreas and kidneys.[13] Von Hippel-Lindau is an autosomal dominant disease in which pancreatic lesions can be the only manifestation for many years. Von Hippel-Lindau is characterized by retinal angiomas, CNS hemangioblastomas, and pancreatic cysts (even cystic replacement of the gland) and is associated with microcystic serous adenoma (Fig. 9) and endocrine tumors of the pancreas.[4],[13]

Annular Pancreas

Annular pancreas is the second most common, yet still rare (~1/10.000 live births), a congenital anomaly

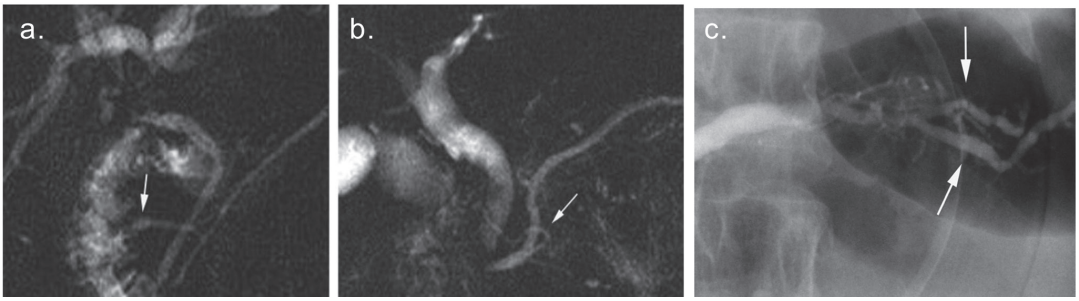

Fig.18. *Variants of ductal anatomy.* ***(a.)*** *MRCP. Dominant duct of Santorini with a present santorinocele (arrow).* ***(b.)*** *Ansa pancreatica* ***(c).*** *ERCP. Presence of two ducts at the tail of the pancreas. [Mortelé, K.J., Multimodality Imaging of Pancreatic and Biliary Congenital Anomalies]*

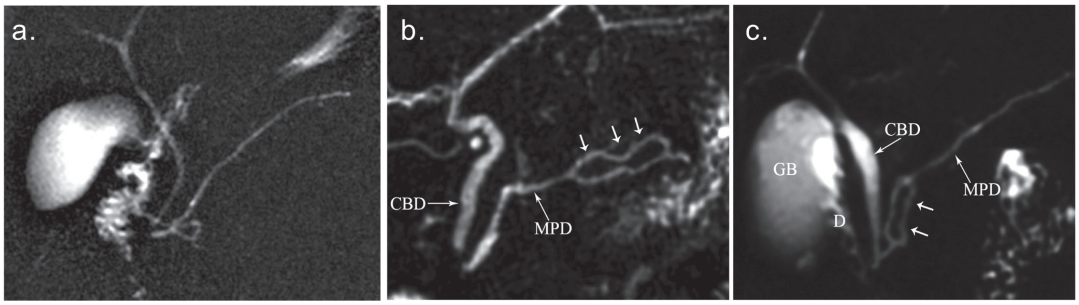

Fig.19. *Variants of ductal anatomy.* ***(a.)*** *MRCP. Ansa pancreatica: a looped branch arising from the duct of Santorini and fusing with the main pancreatic duct that drains into the major papilla. [Kim H. et al., Ansa Pancreatica: A Case Report of a Type of Ductal Variation in a Patient with Idiopathic Acute Recurrent Pancreatitis]* ***(b, c.)*** *MRCP. Duplication of pancreatic duct. CBD: common bile duct, D: duodenum, GB: gall bladder, MPD: main pancreatic duct. [Türkvatan A. et al., Congenital Variants and Anomalies of the Pancreas and Pancreatic Duct]*

in which an incomplete rotation of the ventral anlage leads to a ring of pancreatic tissue circumferentially placed around the second portion of the duodenum (Fig. 10). In approximately 85% of diagnosed cases the annular tissue is situated above the papilla of Vater. [1],[7],[8],[32] Based on morphologic distribution, the annular pancreas has been classified into a complete or incomplete type. Complete refers to a complete encasement of the duodenum by pancreatic parenchyma or annular duct, while the incomplete type demonstrates partial circumferential encasement of the duodenum. The annular pancreatic duct commonly drains in the main pancreatic duct but can communicate with the intrapancreatic common bile duct, the duct of Santorini, or the duct of Wirsung. Histologically, the annular pancreas has been classified into two types: intramural and extramural, based on the presence of pancreatic tissue in the duodenal wall. In the extramural type, the ventral pancreatic duct encircles the duodenum whilst in the intramural type the pancreatic tissue is woven into

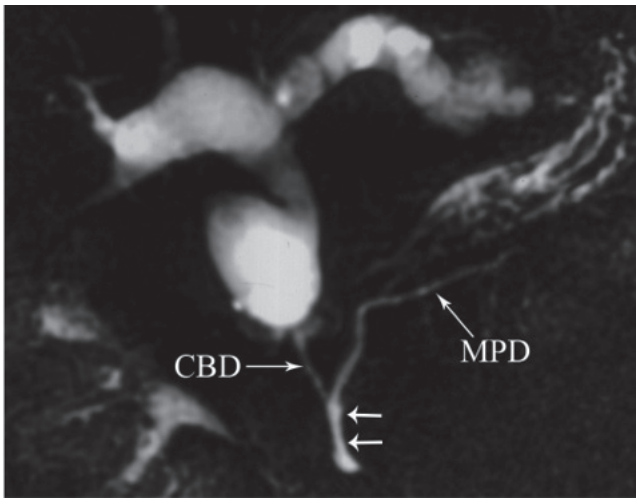

Fig.20. *Anomalous pancreaticobiliary junction* ***(Left)*** *ERCP. Long common channel (arrow) formed by anomalous junction of the common bile duct (CDB) and the main pancreatic duct (MPD). [Alexander L. et al. Congenital Pancreatic Anomalies, Variants and Conditions]* ***(Right)*** *MRCP reveals long common channel (> 15 mm) (arrows) and associated Todani type 4a choledochal cysts with intrahepatic and extrahepatic components. CBD: common bile duct, MPD: main pancreatic duct. [Türkvatan A. et al., Congenital Variants and Anomalies of the Pancreas and Pancreatic Duct]*

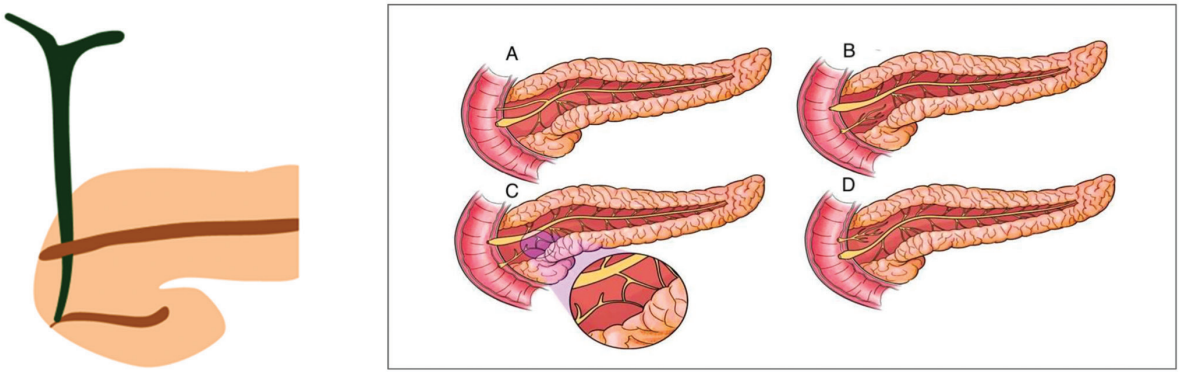

Fig.21. ***(Left)*** *Pancreas divisum. Illustration of ductal anatomy. [Türkvatan A. et al., Congenital Variants and Anomalies of the Pancreas and Pancreatic Duct]* ***(Right)*** *Pancreas divisum configuration types.* ***a.*** *Normal pancreas.* ***b.*** *Classic divisum: no communication exists between the two ducts.* ***c.*** *Incomplete divisum* ***d.*** *Reverse pancreas divisum. [Gutta A. et al, Identification and management of pancreas divisum].*

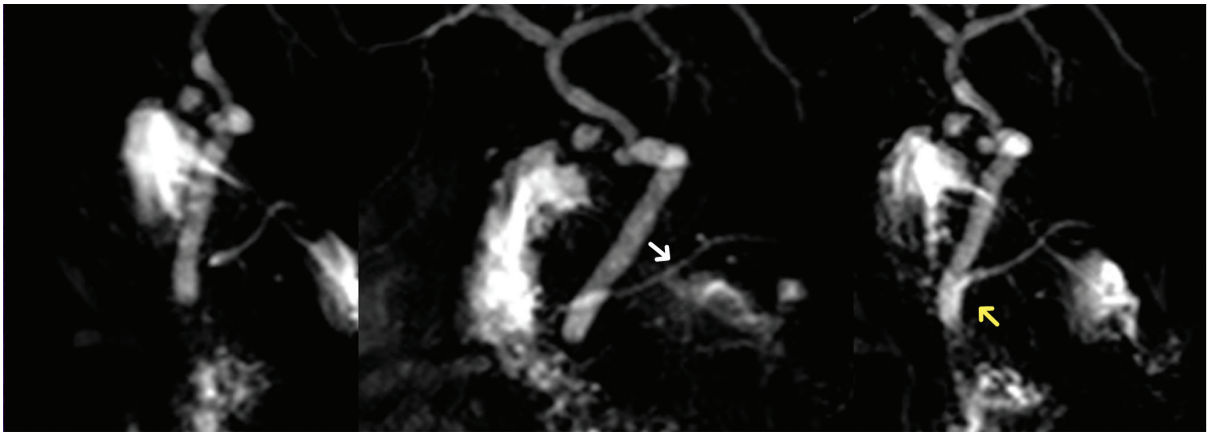

Fig.22. *Pancreas Divisum. MRCP shows a dominant dorsal duct (white arrow) crossing the common bile duct and draining at a superior level, at the minor papilla, where a Santorinicele can also be seen. The duct of Wirsung unites with the common bile duct and drain at the expected site, the major duodenal papilla. (yellow arrow).*

the duodenal wall with evidence of small ducts draining into the duodenum.[32]

Given the rarity of this congenital condition, a precise etiology pertaining to the development of the annular pancreas has not yet been established but the fact that the ventral pancreatic bud is formed in a paired condition, by a right and a left one, is considered of importance in understanding its formation.[7],[32] Amongst many, two major hypotheses have been proposed: complete regression of the left with the adhesion of the right ventral anlage to the duodenal wall which then stretches to form a ring during normal rotation, as proposed by Lecco, and persistence of the left ventral anlage which develops to encircle the duodenum, as proposed by Baldwin (Fig. 11).[4],[7] Overall, there is no debate as to the ventral origin of the annular tissue, as shown by immunohistochemistry studies, and Lecco's hypothesis is favored by some pathologists on the basis of the existence of PP-rich islets on the annular tissue, which is thought to exist in amplitude in the right ventral anlage.[7] A third hypothesis has recently been put forward suggesting adhesion of the tip of the left ventral anlage to the duodenal wall and subsequent "ring-like" development with duodenal rotation.[4] Although not well studied, the role of genetic factors has been linked to this anomaly based on isolated case reports of the familial annular pancreas and over-expression of the ventral-specific gene transmembrane 4 superfamily member 3 (Tm4sf3).

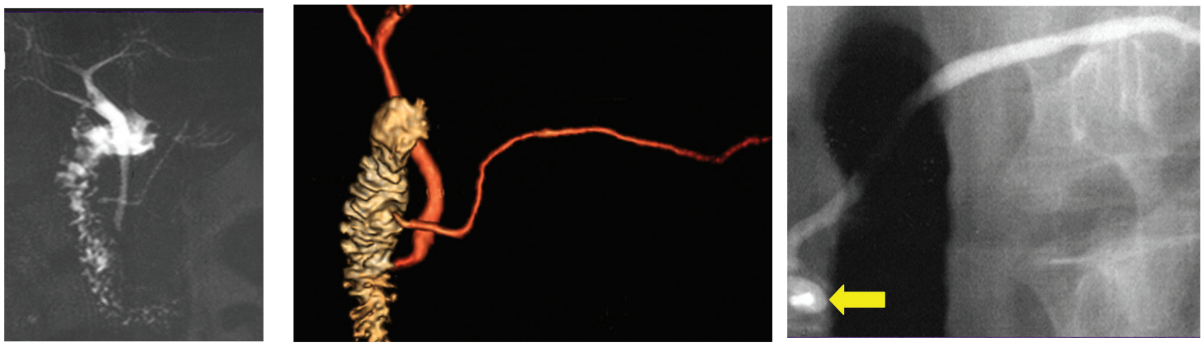

Fig.23. *Pancreas divisum* ***(Left & Middle)*** *MRCP and volume rendered image. The crossing of the dominant duct of Santorini and the common bile duct produces the "crossing ducts" sign.* ***(Right)*** *ERCP. A dominant duct of Santorini drains at the minor duodenal papilla. A cystic dilation of the duct's terminal portion (arrow) can be seen (Santorinicele).*

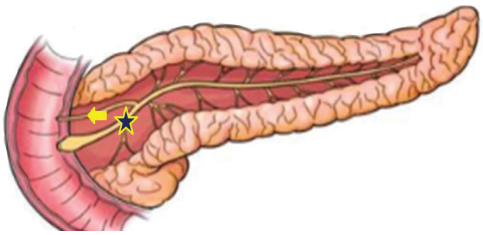

Fig.24. *Pseudo- or false pancreas divisum: An obstruction of the main pancreatic duct of Wirsung downstream to the origin of the duct of Santorini in a, otherwise, normal pancreas. The obstruction can be due to acute pancreatitis, a stricture due to chronic pancreatitis or a malignancy and can mimic the appearance of true pancreas divisum. Pseudo-divisum is important to recognise due to the possibility of malignancy. [Adaptation from Gutta et al.]*

[32],[33] Dysfunction of the Hedgehog signaling pathway has also been suggested as a major molecular contributor to the formation of the annular pancreas, as has Pdx1 (Pancreas and duodenal homeobox gene 1) as a pancreatic-promoting transcription factor expressed in the sites of dorsal and ventral pancreatic bud formation.[33]

Annular pancreas is the most common congenital anomaly of the pancreas presenting in children[33] and more than half of all patients with this type of pancreatic anomaly present as neonates (mean age: 1 day) with symptoms of duodenal constriction and/ or bile duct obstruction (bilious vomiting, abdominal distention, feeding intolerance) and around 70% of them have associated coexisting conditions such as congenital heart defects, duodenal stenosis/atresia, malrotation, tracheoesophageal fistula, renal anomalies, duodenal diverticulum, pancreas divisum, biliary atresia, and anorectal malformations, some of which occur in the spectrum of aneuploidies like Down syndrome.[1],[2],[32],[33] Maternal polyhydramnios have also been associated with the fetal annular pancreas.[33] Other infants with minimal or non-existent constriction can remain asymptomatic lifelong and a small fraction will become symptomatic between the third and sixth decade of life (median age: 47 years) with symptoms of abdominal pain, duodenal obstruction and ulceration, and pancreatitis. [1],[32],[33] Duodenal obstruction occurs secondary to either the encasement of the duodenum or to scarring, stenosis, or the presence of duodenal webs (Fig. 12). The pathogenesis of pancreatitis in the setting of annular pancreas remains unclear and when it occurs, is usually confined to the annulus and the adjacent pancreatic head sparing the body and tail of the gland.[32] In the adult population, 30% have associated pancreas divisum and only 16% are associated with congenital anomalies. Men have been found to be more frequently affected than women [33] and pancreaticobiliary neoplasms occur at higher rates in patients with annular pancreatic appearance, however, causality has not yet been determined.[1],[2]

The diagnosis of the annular pancreas is radiologic and usually made incidentally or on the evaluation of clinical manifestations.[32],[33] Prenatally, it can be di-

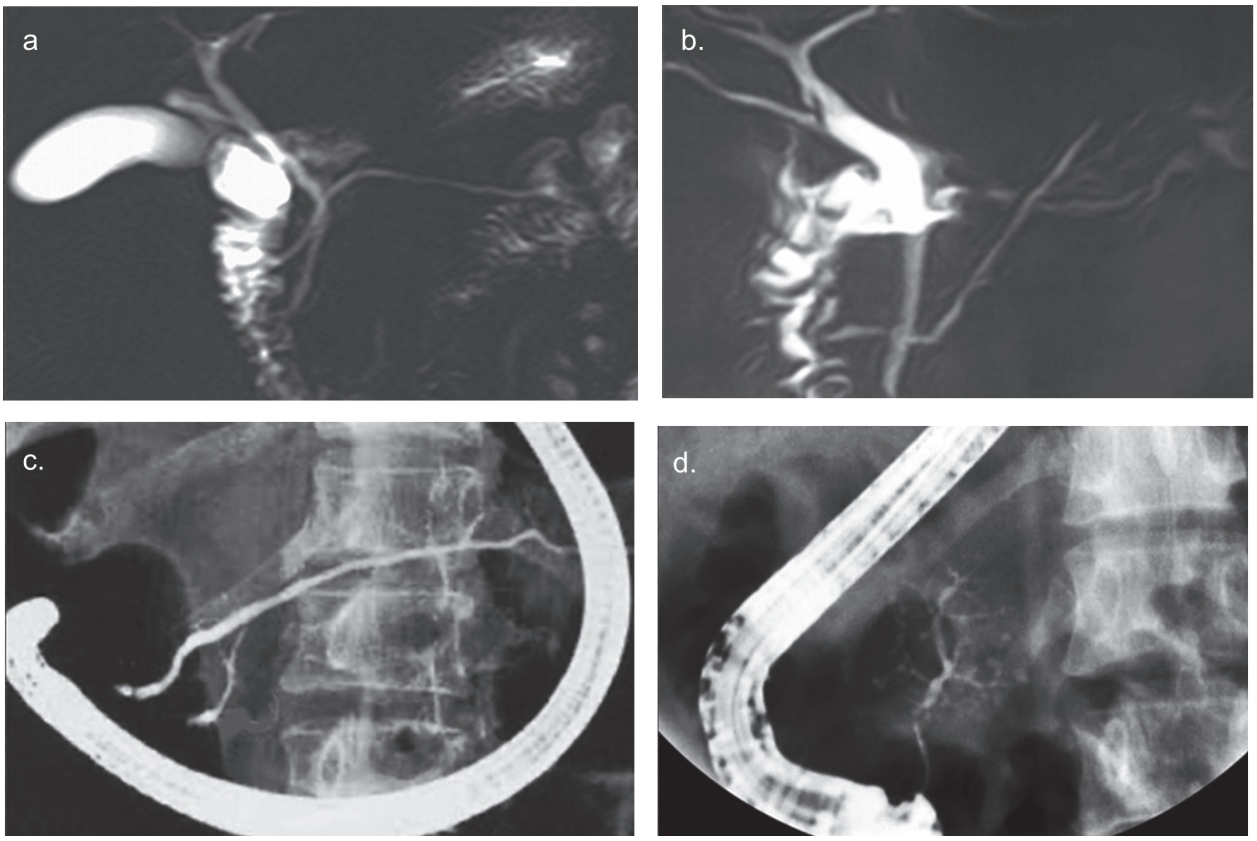

Fig.25. (a, b.) *MRCP. The "crossing ducts" sign. The dominant dorsal duct crossing the intrapancreatic common bile duct to drain into the minor papilla.* ***(c, d.)*** *ERCP. Pancreas divisum: the dominant dorsal pancreatic duct and the smaller ventral emptying separately in the duodenal wall.*

agnosed by ultrasonography while in infants with signs and symptoms of intestinal obstruction by ultrasonography or plain abdominal radiographs, which show a "double bubble" sign pertaining to the obstructed stomach and duodenal bulb: the larger proximal bubble is caused by gastric distention and the smaller distal by the dilated duodenal bulb (Fig. 12).[32],[33] The "double bubble" sign however is nonspecific for annular pancreas.[32] CT and MR imaging reveal the annular tissue with enlargement of the pancreatic head and in cases of the partial type, the incomplete encircling of the descending duodenum anteriorly and posteriorly which resembles a crocodile jaw and is, thus, characterized as the "crocodile jaw appearance"(Fig. 13).[37] The annular duct in the extramural type passing posteriorly and wrapping around the descending duodenum can be well visualized on MRCP and ERCP (Fig.13).[13] In a study published in 2009 in the American Journal of Radiology by Sandrasegaran et al., the authors' findings suggest that a complete ring of pancreatic tissue around the duodenum is not required for a diagnosis of the annular pancreas as more than one-third (37.5%) of patients in this study had a radiologically incomplete annulus on images with a subsequent ERCP or surgical confirmation of annular pancreas. An imaging finding, however, of pancreatic tissue extending in a posterolateral direction to the second part of the duodenum ("crocodile jaw" configuration) in the appropriate clinical setting (chronic pancreatitis or gastric outlet obstruction), should raise the suspicion of the annular pancreas. The authors lastly suggest that secretin-enhanced MRCP may be the best noninvasive method of assessing ductal anatomy and should be considered when the diagnosis of the annular pancreas is entertained (Fig.14).[34]

Circumportal or portal annular pancreas is a type of annular arrangement where tissue from the uncinate

process anomalously encases the portal and/or the superior mesenteric or splenic veins.[2] The reported prevalence in the literature ranges from 1.4-2.5%, making this annular variant less uncommon than thought.[16],[17]

It has been suggested that, embryologically, a circumportal pancreas forms as a result of the deviant fusion of the developing uncinate process of the ventral bud with tissue from the dorsal pancreatic bud that leads to entrapment of the portal venous confluence.[2],[16] With regards to the relation between the fusion site and the splenic vein, the annular variant is classified as suprasplenic, infrasplenic or mixed and further as anteroportal or retroportal, on the basis of the course of the main pancreatic duct (Fig 15).[17]

The circumportal pancreatic morphology bears clinical significance in the setting of preoperative planning for pancreatic resection and is typically asymptomatic.[2],[8],[16] CT and MR scans demonstrate the continuity of the uncinate process with the pancreatic body in two or more consecutive slices as well as the course (retroportal/anteroportal) of the main duct, although better depicted on contrast-enhanced images. The high prevalence (~25%) of concomitant variant hepatic arterial anatomy (replaced right hepatic artery arising from the superior mesenteric artery, replaced left hepatic artery arising from the left gastric artery, and anomalous course of the common hepatic artery), makes contrast-enhanced scans superior in assessing for such anatomical variants prior to a pancreatic resection (Fig. 16).[16],[18]

Pancreatic Ductal Variants & Ansa pancreatica

Developmental anomalies during fusion of the ventral and dorsal pancreatic ducts can result in a number of possible variations in their course, leading to an absent duct of Santorini, bifid configuration with dominant drainage from the duct of Santorini, pancreas divisum or ansa pancreatica among others (Fig. 17).[20]

Ansa pancreatica is the least common anatomic variant. The true prevalence is not known but it is estimated through various studies between 0.5% and 1.2%.[20],[21] This "handle" between the two ducts arises from the obliteration of the accessory duct at the proximal end of its junction with the MPD and replacement by a reversed "S-shaped" loop that drains at or near the minor papilla. It is also possible that this looped duct does not have an orifice in the duodenum. Two subtypes have been described, the classic "S-shaped" loop and a looping duct connecting the distal part of the duct of Wirsung with a patent duct of Santorini; for the second subtype, however, a debate has been made as by some it is classified under the group of disorders called the meandering pancreatic duct.[21]

Ansa pancreatica has been established as a predisposing factor for recurrent acute pancreatitis, particularly in the setting of chronic alcohol consumption.[23] MRCP can non-invasively visualize the variants of ductal anatomy, although ERCP is more accurate due to higher intraductal pressure (Fig. 18).[21],[24]

Anomalous pancreaticobiliary junction

Anomalous pancreaticobiliary junction (APBJ) refers to a rare congenital anomaly (1.5-3% of patients undergoing ERCP for various reasons) in which the junction of the biliary and pancreatic ducts occurs before entering the duodenal wall.[2],[7] As a result, a common long channel is formed of at least 15mm and a malformed sphincter of Oddi encircles the common channel within the pancreatic head.[2],[4] In the absence of the normal sphincteric function of the muscles that comprise the Oddi apparatus, reflux of pancreatic and biliary secretions cannot be prevented. The reflux can be pancreaticobiliary or biliopancreatic depending on the type of junction.[2] The elevated intraductal pressure together with the reflux and stasis of pancreatic juice renders APBJ a predisposing factor for recurrent episodes of pancreatitis, gallbladder, and biliary tract cancer.[2],[4],[7]

APBJ is also commonly associated with congenital bile duct dilation and is therefore classified into two groups, with or without bile duct dilation. Over 90% of the patients with type I and IVa choledochal cysts exhibit also APBJ.[7] Embryonic disarrangement of the distal bile and ventral pancreatic ducts with an oblique position before fusion, a dysplastic ventral pancreatic bud, arrest of migration of the pancreaticobiliary ductal junction inside the duodenal wall between the seventh and eighth week of gestation or failure of ampullary involution are some of the hypotheses on the cause of

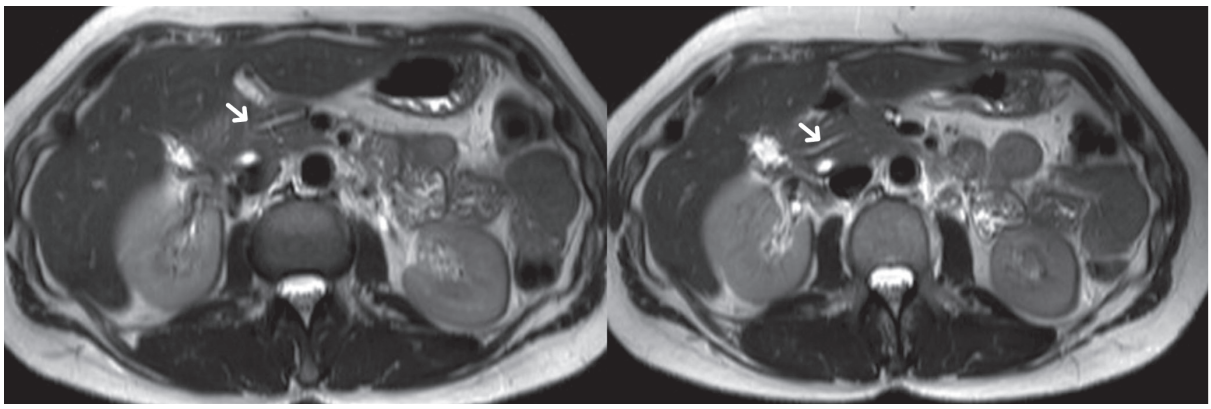

Fig.26. *Pancreas Divisum. MR image shows the dorsal pancreatic duct (white arrow) crossing anteriorly to the common bile duct, towards a different drainage site: the minor duodenal papilla.*

APBJ with or without choledochal cysts.[7],[25] It is of note that higher rates of biliary tree malignancies are observed in APBJ patients without bile duct dilation (42.4% versus 21.6%).[2]

Although combining MRCP and CT images improves the diagnostic accuracy of both methods, ERCP establishes the diagnosis by demonstrating the union of CBD and the duct of Wirsung more than 15mm from the duodenal papilla (Fig. 20).[1]

Pancreas Divisum

Pancreas divisum, appearing in almost 14% of the population, is the most common pancreatic anomaly and represents a true failure of fusion of the ventral and dorsal duct.[1],[7] The ventral duct of Wirsung eventually drains only a part of the pancreatic head (ventral pancreas) while the dorsal duct of Santorini drains the majority of the gland, through the minor papilla (Fig.21).[8] While an absent or a nonfunctional accessory duct and/or sphincter of Helly at the minor duodenal papilla is a common configuration in the general population, patients with pancreas divisum rely on these anatomical structures for primary drainage.[2] A variety in the degree of failure in ductal fusion is responsible for the three main subtypes of pancreas divisum: complete, which represents 70% of all cases, where there is no communication between the two ductal systems (Fig.21b). Incomplete, with a prevalence of 15%, where a filamentous communication persists between the two ducts and finally, a rare, reverse pancreas divisum variant, where the duct of Santorini does not communicate with the main pancreatic duct, leading to isolation of a small component of the dorsal pancreas (Fig. 21c).[13],[38]

Even though the clinical significance of pancreas divisum is still debated upon as most patients remain asymptomatic (in 95% of cases the anomaly is found incidentally on abdominal imaging for an unrelated indication) [1],[38], the incidence of divisum increases in patients with recurrent acute or chronic pancreatitis, ranging from 25-38% [13]; an etiological relationship can therefore be suspected, reflecting poor ductal drainage through a stenotic minor papilla and increased intraductal pressure. Manometric studies have indeed shown minor papilla and dorsal duct hypertension, owing possibly to a transient obstruction of the minor papilla by proteinaceous material in pancreatic secretions.[38] As a result of this defective drainage, a santorinicele (cystic dilation of the terminal portion of the duct of Santorini) can sometimes be identified on MRCP or ERCP (Fig. 22,23).[2] It is of note that in cases of pancreatitis with pancreas divisum, isolated dorsal pancreatitis accounts for a much higher percentage and that complete divisum configuration with dorsal pancreatic duct obstruction might stand as a factor that promotes oncogenesis.[29],[30] In the setting of reverse divisum, gallstone obstruction of the major papilla can lead to severe pancreatitis as the majority of the gland depends on the major papilla for drainage, unlike the other two variants.[38]To avoid conditions that can mimic pancreas divisum such as pseudo/false pancreas divisum (Fig. 24) [38], it is important to clearly identify the anomaly's key anatomical fea-

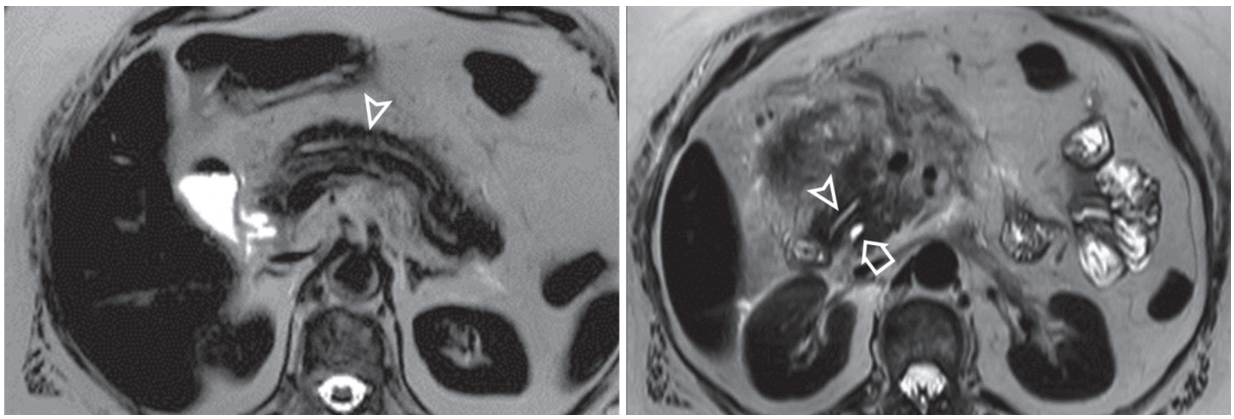

Fig.27. *Pancreas Divisum. MR image shows the dorsal pancreatic duct in continuity with the duct of Santorini (white arrowhead) crossing anterior to the common bile duct (white arrow), draining at two different sites.*

tures: continuity of the dorsal duct with the duct of Santorini and drainage at the minor papilla, at a level superior to that of bile duct drainage; separate ventral duct drainage at the expected site and, in most cases, no communication can between the two ducts. This configuration is responsible for the "crossing ducts" sign, which refers to the appearance of a dominant dorsal duct running across anteriorly and superiorly to the intrapancreatic common bile duct, best visualized on maximum intensity projection MRCP images (Fig. 23,25,26,27).[31] MRCP offers high sensitivity and specificity, and secretin injection further increases the method's diagnostic accuracy in assessing ductal morphology, including santorinicele. Contrast-enhanced CT allows for the concurrent assessment for signs of pancreatitis, but pancreatic disease and its complications lower the modality's sensitivity as ductal configuration can be obscured.[38] ERCP represents still the imaging modality of choice for a definitive diagnosis, offering the possibility of therapeutic minor papillotomy (with or without stenting of the accessory duct) in patients with recurrent acute pancreatitis, severe acute pancreatitis, chronic pancreatitis, and chronic abdominal pain of pancreatic origin.[1],[4],[13],[38] **R**

Conclusion

Understanding embryonic development of the pancreas is essential in the process of deciphering the pathogenesis of congenital pancreatic disease which is, ultimately, visualized and expressed as imaging findings to radiologists. Familiarity with these anomalies and their radiological traits facilitates differential diagnosis and increases diagnostic accuracy.

Conflict of interests

The authors declared no conflicts of interest

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