

ORIGINAL PAPERS

Agensis of the dorsal pancreas: systematic review of a clinical challenge

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ABSTRACT

Background: Agensis of the dorsal pancreas is a rare malformation. Since 1911 and until 2008, 53 cases have been reported. Several authors have recently described the association of this anomaly with neoplasia of the ventral pancreas, thus we performed a systematic review of the literature from 2008 to 2015.

Methods: A systematic review of the Medline and ISI Web of Science Databases from 2008 until 2015 was carried out, and 30 articles which met the inclusion criteria were identified that included a total of 53 patients: 7 children and 46 adults.

Conclusions: Although dorsal pancreatic agensis is a rare malformation, given its association with non-alcoholic pancreatitis and neoplasia of the residual pancreas, physicians should maintain an expectant attitude.

Key words: Dorsal agensis of the pancreas. Short pancreas. Diabetes mellitus. Mucinous cyst. Pancreas anomaly.

INTRODUCTION

Dorsal pancreatic agensis (DPA) is a very rare malformation which consists of the absence of the neck, body and tail of the pancreas derived from the bud of the dorsal endoderm (1,2). This anomaly was first described in 1911, and 53 cases were reported up to 2008 (3,4). Several authors have reported an association between DPA and acinar-ductal metaplasia (ADM), and neoplasia of the remnant pancreas (ventral pancreas) and diabetes (5-9).

The purpose of this systematic review was to evaluate the clinical features and pathologic findings of patients with DPA following on from seminal study by Schnedl (4).

METHODS

Search strategy

We searched the medical literature using a comprehensive text word and MESH-based electronic search of MEDLINE and

EMBASE; the Pub Med database and Scopus was queried including the terms: *dorsal pancreatic agensis, short pancreas, pancreatic agensis, pancreatic hypoplasia, pancreatic anomaly and pancreatic aplasia* from 1998 until December 2015, excluding all the cases previously reported by Schnedl (4). Additionally, the references of relevant articles were hand searched for additional material. The search included abstracts, case-series, case reports, editorials, letters to the editor, and images in gastroenterology. We excluded review articles, studies reporting on fetuses, research animals, those in which clinical and pathologic data were missing, letters related to reported cases or those where the full text or abstract was not written in English, Spanish, French or German. The search was performed by the two authors –JAC and JS– and the results were contrasted with one of the senior authors (FR).

Eligibility criteria and data collection

All reports on DPA were included, which described at least 1 case. Full-text articles were obtained to clarify the potential eligibility and the selected studies were evaluated in accordance with the Preferred reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (10). Two authors (JAC, FR) independently assessed the studies selected and extracted the following data: first author, year of publication, country of origin, number of patients, age, gender, type of clinical presentation, associated disorders, genetic analyses, radiologic characteristics, treatment undertaken and pathology report.

RESULTS

In total 1,021 articles were retrieved from the primary database search and 54 articles were retrieved by manual cross-search of the reference list. Following removal of duplicates, 293 articles were assessed for further analysis; screening of the titles and abstracts enabled us to exclude 240 articles. The full-text articles of the remaining 41 studies were assessed for eligibility; we then excluded

Received: 03-06-2016

Accepted: 03-06-2016

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Cienfuegos JA, Rotellar F, Salguero J, Benito A, Solórzano JL, Sangro B. Agensis of the dorsal pancreas: systematic review of a clinical challenge. *Rev Esp Enferm Dig* 2016;108(8):479-484.

DOI: 10.17235/reed.2016.4474/2016

all reviews, commentaries on published cases and those studies not meeting the requirements for DPA: short pancreas or pancreatic hypoplasia. We excluded the cases of complete agenesis of the pancreas (3 articles), the so-called short pancreas (5 articles) and others reported as atrophy of the body and tail. A flow chart of the literature search is shown in figure 1. Overall 30 articles met the inclusion criteria and these reported on 53 patients; 7 children and 46 adults. The disorders associated with the 53 cases reported since 2008 are summarized in table I (5-9,11-34).

Abdominal pain and diabetes mellitus were the most frequent clinical manifestation in 10 patients. Nine of the 53 patients underwent total pancreatectomy mainly for adenocarcinoma of the pancreas (Table I). Notably 4 cases were incidentally diagnosed.

DISCUSSION

DPA is a rare malformation caused by the absence of the dorsal pancreatic bud of the endoderm (1,35,36). The entity was first described by Heiberg in 1911 (3) and since then until 2008 53 cases have been reported by Schnedl (4) in 2009. From 2008 to 2015, we have identified 53 cases, 7 in children and 46 in adults. The high number of cases reported (53) in the last 8 years merits special mention, especially as in the previous 100 years (1911-2008) Schnedl only identified 53 cases. This may be due to the greater accessibility to imaging techniques.

The clinical manifestations of DPA reflect the abnormalities in the embryogenesis of the dorsal pancreas. The

exocrine and endocrine tissues of the pancreas come from a common pool of multipotent progenitor cells from the foregut which give rise to the trachea, lungs, esophagus, stomach, thyroid, liver, bile ducts and the pancreas (36-38).

In humans the initial bud of the pancreas is produced on day 26 of gestation (G 26d) with the dorsal bud and the two ventral buds forming on day 30 (G 30d) (Fig. 2). The left ventral bud regresses whilst the right ventral bud migrates posteriorly together with the rotation of the gut at 6-7 weeks of gestation (G 6-7w) and fuses with the dorsal bud. With the fusion of both buds, morphogenesis and differentiation begin in the acinar, ductal and endocrine cells (1,35,37,38).

The ventral and dorsal buds share specific signaling pathways and transcription factors (TF) such as Hedgehog, via Notch or TF: fibroblast growth factor-10 (FGF-10), epidermal growth factor (EGF), retinoic acid, Wnt signaling and bone morphogenetic protein (BMP) produced by the surrounding mesoderm (39).

The transition from multipotent progenitor cells in an organ with exocrine secreting units and endocrine tissue is a strictly regulated multi-sequential process. As pancreatic morphogenesis progresses, the TF are more selective for the 3 cell lines: bHLH neurogenin 3 (Ngn3) for β cells, SOX9 for ductal cells and PTF1 for acinar cells.

A detailed description of pancreatic embryogenesis is beyond the scope of this study and several excellent reviews are available (1,35-37,40-42).

The clinical presentation of DPA varies greatly ranging from incidental detection on X-ray, surgery or autopsy through to the development of a ductal adenocarcinoma of the pancreas (4,5). Diagnosis requires confirmation of the absence of the neck, body and tail of the pancreas and duct of Wirsung using endoscopic retrograde cholangiopancreatography (ERCP) or MRCP (Figs. 3 and 4). DPA has been reported both in children and adults and may be associated with an autosomal dominant mutation of the hepatocyte nuclear factor 1B (HNF1B) gene, although in most cases it is sporadic (43-45).

Abdominal pain and diabetes are the most frequent clinical manifestations reflecting exocrine and endocrine insufficiency as most of the islands of Langerhans are located in the tail of the pancreas (4,19,46,47).

The association between cystic lesions and non-alcoholic chronic pancreatitis with pancreatic ductal adenocarcinoma (PDA) has recently been highlighted by Rittenhouse et al. (5), in 3 patients who also presented dorsal pancreas agenesis. Other authors have reported an association with ampullary adenocarcinoma and intraductal papillary mucinous neoplasm (IPMN) (6,26). There have also been reports of an increase in the size of the remnant pancreas and recurrent acute pancreatitis as a form of presentation (48).

These findings confirm the development of phenomena related to a reparative response in the residual pancreas. In experimental models of acute pancreatitis and in partial

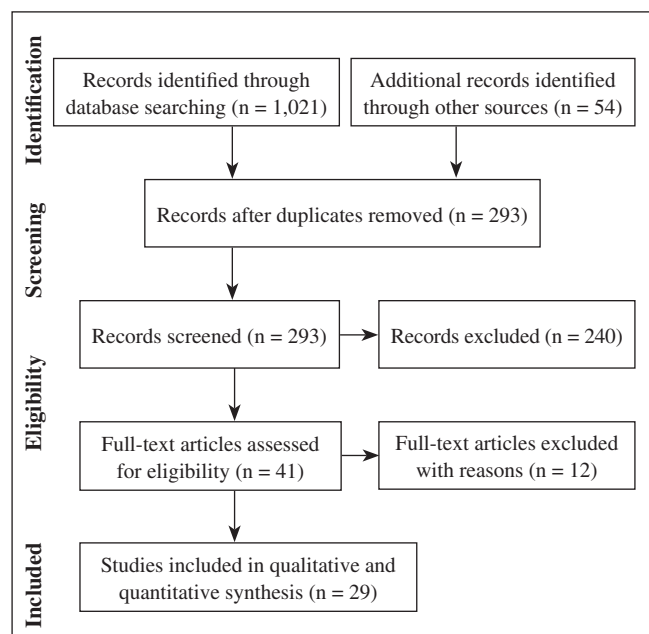


Fig. 1. Flow chart of the systematic literature search (adapted from ref. 10).

Table I. Demographics of the selected studies

<i>Author, year reported (Ref. *)</i>	<i>n</i>	<i>Age (y) / Sex (M/F)</i>	<i>Clinical presentation</i>	<i>Associated diseases</i>	<i>Pancreatic head desc.</i>	<i>Cause mutation</i>	<i>Surgical procedure</i>
Doxey et al. (11)	1	8/M	Steatorrhea	Exocrine panc. insufficiency	Normal	Not assessed	
Chen et al. (12)	3	4w/M; 4w/F; 2w/M	Neonatal DM	Exocrine panc. insufficiency	Normal	Not found	
Haldorsen et al. (8)	5	15/M; 38/F; 62/F; 6/F; 38/M	DM	Exocrine panc. dysfunction	Slightly atrophic	HNF1B	
Pasaoglu et al. (13)	1	62/F	Incidental finding	Mild elevat. fasting glucose	Normal	Not assessed	
Sakpal et al. (6)	1	49/M	Recurrent pancreat. Weight loss	Mucinous adenocarcinoma	Cystic mass 5.4 cm	Not assessed	Total pancreatect.
Kin et al. (14)	1	38/M	Incidental finding	Not reported	Normal	Not assessed	
Rittenhouse et al. (5)	3	37/F 59/F 68/M	DM DM, abdominal pain Abnormal liver function test	Pancreatic calcification Pancreatic calcification Pancreatic calcification	3 cm adenocarcinoma 8.5 x 6 cm adenocarcinoma 2.1 cm adenocarcinoma	Not assessed Not assessed Not assessed	Total pancreatect. Total pancreatect. Total pancreatect.
Low et al. (15)	1	62/F	Abdominal pain	Polysplenia, preduodenal portal vein, choledocholithiasis	Normal	Not assessed	Cholecystectomy, choledocholithotomy
Kapoor et al. (16)	1	55/M	Cholangitis, weight loss	Ampullary carcinoma	Mass in ampulla	Not assessed	Total pancreatect.
Mohapatra et al. (17)	3	30/M 35/F 35/F	DM DM Abdominal pain	Polysplenia Polysplenia	Normal Enlarged calcifications Enlarged	Not assessed Not assessed Not assessed	Insulin therapy Insulin therapy Panc. enzyme sup
Sebestain et al. (18)	1	27/M	Recurrent pancreatitis		Normal	Not assessed	Medical treatment
Lang et al. (19)	1	65/M	Abdominal pain, DM 2		Small calcifications	Not assessed	Medical treatment
Jeong et al. (34)	1	49/F	Acute pancreatitis	Polysplenia, preduodenal portal vein	Enlarged	Not assessed	Medical treatment
Dumitrascu et al. (20)	1	44/F	Jaundice Abdominal pain		2.8 cm adenocarcinoma	Not assessed	Total pancreatect.
Shimodaira et al. (21)	1	19/M	Glycosuria		Normal	Not assessed	Insulin therapy
Chaudhary et al. (22)	1	43/M	Acute pancreatitis		Pseudocyst	Not assessed	Medical therapy
Bento et al. (23)	1	59/F	Acute pancreatitis		Enlarged	Not assessed	Medical therapy
Oki et al. (24)	1	65/M	Back pain		Adenocarcinoma	Not assessed	Total pancreatect.
Vijayaraghavan et al. (25)	6	15/M; 20/M; 24/F; 20/M; 20/F; 16/M	DM (2)		Not reported	Not assessed	Not reported

(Continue in the next page)

Table I (Cont.). Demographics of the selected studies

Author, year reported (Ref. *)	n	Age (y) / Sex (M/F)	Clinical presentation	Associated diseases	Pancreatic head desc.	Cause mutation	Surgical procedure
Cho et al. (9)	11	72/M; 79/F; 71/F; 36/F; 72/F; 41/F; 63/M; 36/F; 81/M; 49/M; 61/F	DM (5) Abdominal pain (7)		Not reported	Not assessed	Not reported
Sannappa et al. (26)	1	51/F	Jaundice Weight loss		3 cm adenocarcinoma	Not assessed	Total pancreatect.
Zhou et al. (27)	1	56/M	Incidental finding		Enlarged	Not assessed	Not reported
Lim et al. (28)	1	28/F	Incidental finding		Normal	HNF1B	Medical treatment
Thakur et al. (29)	1	42/M	Abdominal pain	Cholelithiasis	Normal	Not assessed	Cholecystectomy
Mistry et al. (7)	1	42/M	DM; jaundice		Ampullary carcinoma	Not assessed	Total pancreatect.
Lal et al. (30)	1	45/F	Abdominal pain	Pancake kidney Bicornuate uterus	Normal	Not assessed	Medical treatment
Kumar et al. (31)	1	35/M	Acute pancreatitis		Enlarged	Not assessed	Medical treatment
Sahoo et al. (32)	1	47/F	Abdominal pain Diabetes	Cholelithiasis Malrotated kidney	Normal	Not assessed	Not reported
Guimaraes et al. (33)	1	57/F	Jaundice	Choledocholithiasis	Normal	Not assessed	ERCP

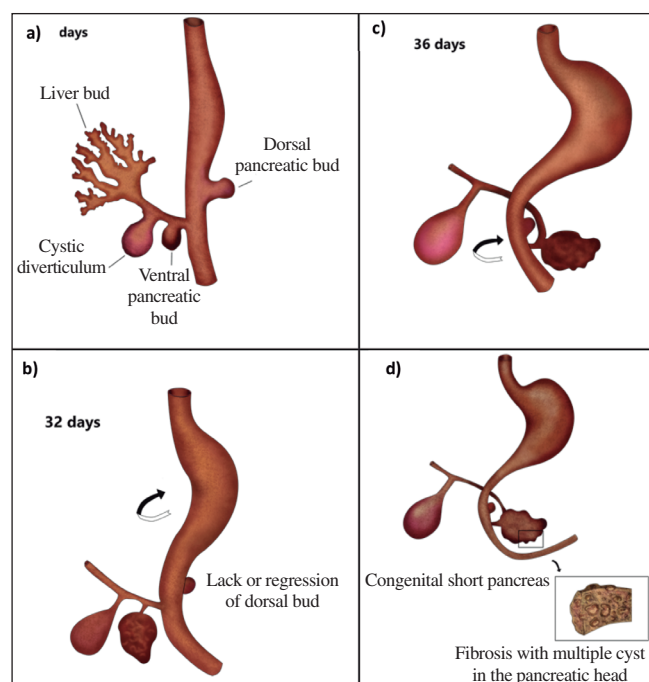


Fig. 2. Organogenesis of the pancreas from ventral and dorsal endoderm buds, showing the lack of dorsal pancreas. Note that figure 1 shows the cystic formation and fibrosis in the remnant pancreas. See inset for an enlarged cutaway view of the ventral pancreas.

resections of the pancreas, regeneration of the pancreas has been reported in mice and children with nesidioblastosis, but never in adults (41,48,49). In the regenerative response of the pancreas, the presence of acinar-ductal metaplasia has been reported where there is an upregulation of ductal markers such as CK19 and SOX9. In mouse models, the development of PDA with a ductal phenotype has been confirmed. This is consistent with the clinical findings of Rittenhouse (5,50).

CONCLUSION

Although DPA is a very rare malformation, given its association with non-alcoholic chronic pancreatitis and neoplasms of the residual pancreas (the ventral pancreas), physicians should maintain an expectant attitude.

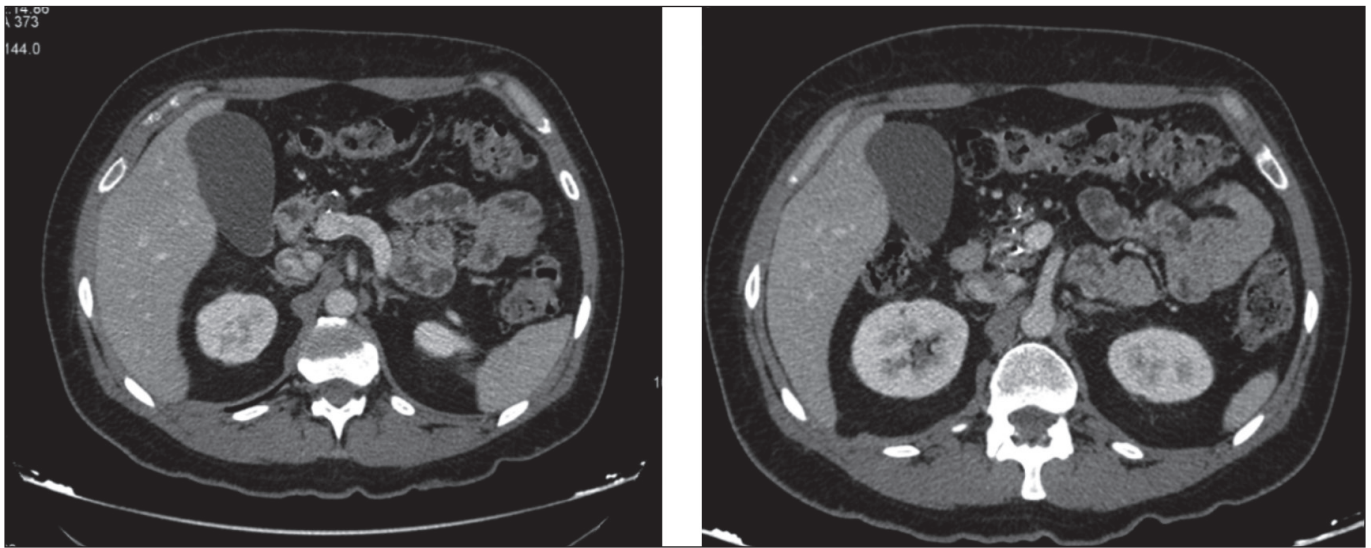


Fig. 3. Axial images from contrast-enhanced CT showing the absence of pancreatic tissue or duct in the neck, body and tail. A 40-year old male presented with a 20-year history of chronic idiopathic cholestasis and carbohydrate intolerance. Three cystic lesions with calcifications were observed in the head of the pancreas.

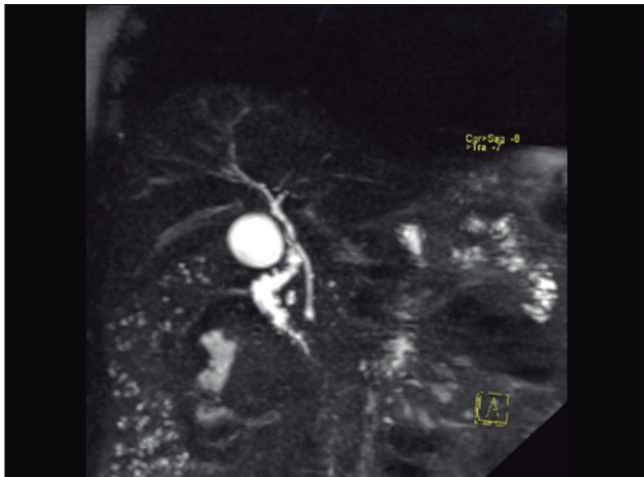


Fig. 4. Coronal heavily T2-weighted reconstruction MRCP image showing small cysts with calcification in the head of the pancreas. The pancreatic duct and dorsal pancreas is not observed.

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