THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

MEDICINE
Case report

PANCREAS DIVISUM MAY BE INVOLVED IN THE OCCURENCE OF RECCURENT PANCREATITIS AND SECONDARY OF DIABETES MELLITUS-CASE REPORT

Adrian DIJMĂRESCU[1,2], Alina NICOLAU[3], Rucsandra Elena DĂNCIULESCU MIULESCU[1,3] and Cristian GUJA[1,3]
[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]"Fundeni" Clinical Institute, Bucharest, Romania
[3]"N.C.Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania

Corresponding author: Rucsandra Elena Dănciulescu Miulescu
5-7 Ion Movila Street, Bucharest, District 2, Postal Code 11420, E-mail: rucsandra_m@yahoo.com

Accepted September 12, 2019

Pancreas divisum is a congenital variation of the pancreatic duct anatomy, generated by the complete or partial fail of the embryological ventral and dorsal buds' fusion during fetal development. Most subjects with pancreas divisum are asymptomatic, but some studies suggest that the condition is involved in the occurrence of recurrent episodes of pancreatitis which could develop into chronic pancreatitis and secondary diabetes mellitus. *Case report*. We describe the clinical case of a 37-year old Caucasian male diagnosed in 2005 with chronic recurrent pancreatitis associated with pancreas divisum. The patient had 25 acute episodes of the condition, last episode in 2018, and secondary diabetes mellitus from 2008. At diabetes diagnosis, the patient received treatment with gliclazidum. In 2014 the patient was admitted in hospital with elevated glycemic values, polyuria, polydipsia, reason for which basal bolus insulin therapy was initiated. The patient has a family history of diabetes (father and grandmother), is smoker and drinks alcohol in excess. Lifestyle optimization measures (diet, exercise, smoking and alcohol cessation) and insulin dose adjustments were recommended. *Conclusion*. Diabetes mellitus is a frequent complication of recurrent acute pancreatitis and chronic pancreatitis. The management of diabetes secondary to pancreatic diseases require lifestyle optimization measures and glucose lowering therapy (frequently insulin is required) but also treatment of the exocrine pancreas insufficiency with pancreatic enzyme replacement which can prevent malnutrition and metabolic complications.

Key words: pancreas divisum, reccurent pancreatitis, secondary diabetes mellitus.

INTRODUCTION

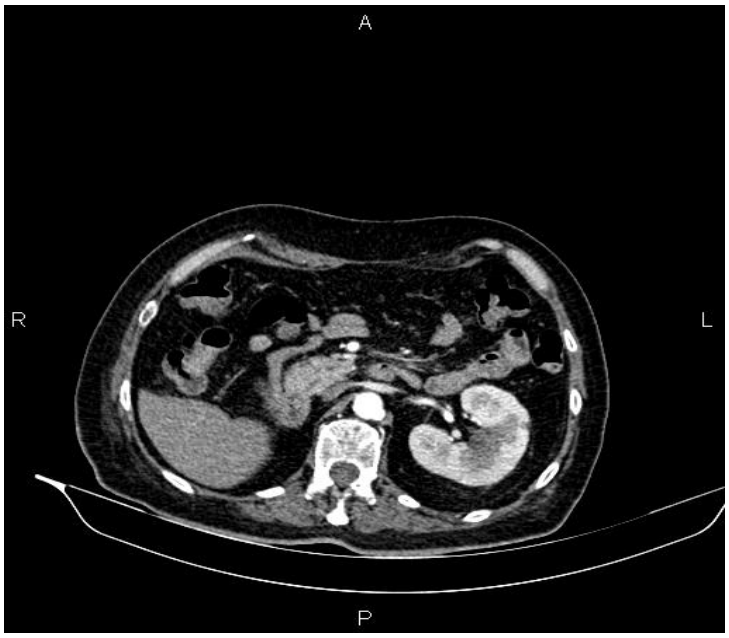
Pancreas divisum is a congenital variation of pancreatic duct anatomy, generated by the complete or partial fail of the ventral and dorsal buds' fusion during fetal development[1]. The condition occurs in 4–14% of the population[2].

In the normal embryological pancreas development, the fusion of ventral and dorsal buds generates the duct of Wirsung, the principal pancreatic duct, which drains to the ampulla of Vater and supplies pancreatic juice provided from the exocrine pancreas. The duct of Wirsung joins the common bile duct before to the ampulla of Vater, after which the ducts perforate the duodenum at the major duodenal papilla[1,3]. In the absence of fusion, the dorsal duct becomes the main pancreatic duct, also referred to as the duct of Santorini and drains most of pancreas into the duodenum through the minor papilla[4]. Three forms of the pancreas divisum are described:

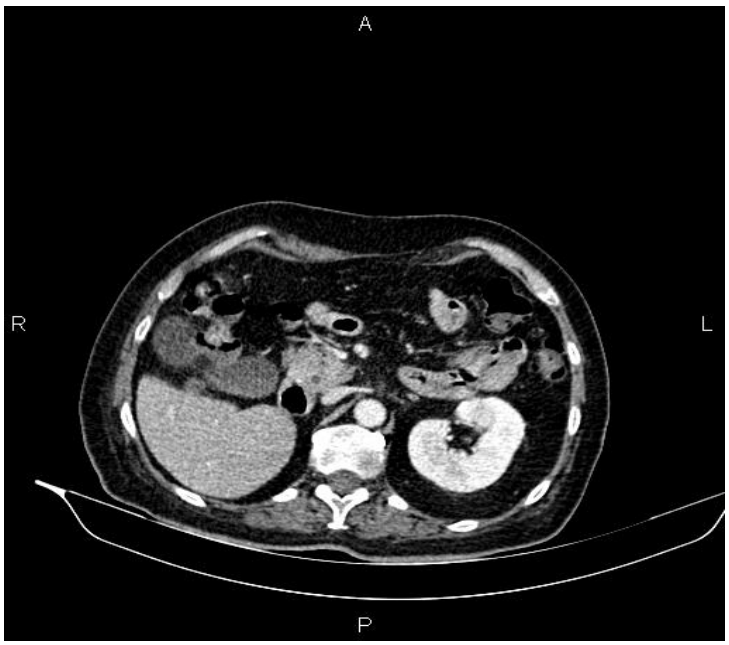
- type I is a complete failure of the ventral and dorsal buds to fuse;
- type II is characterized by the absence of the ventral duct;
- type III presents a small communication between the ventral and dorsal duct[3].

Images of type I and II pancreas divisum evidenced by computed tomography (CT) and nuclear magnetic resonance (MRI) is shown in Figure 1 and 2.

Most subjects with pancreas divisum are asymptomatic, but some studies suggest that the condition is involved in the occurrence of recurrent acute pancreatitis which could develop into chronic pancreatitis and secondary diabetes mellitus[3,4]. Regarding the diagnosis/definition of these conditions, in an article published in 2017, Kuzel AR and collaborators mention that "*acute pancreatitis is defined as the presence of any two symptoms including: abdominal pain radiating to the back, serum lipase >180 U/L, and radiological evidence of inflammation of the pancreas. Recurrent pancreatitis is defined as two or more episodes of acute pancreatitis. Chronic pancreatitis can be diagnosed with the presence of calcifications on computed tomography"* [3].

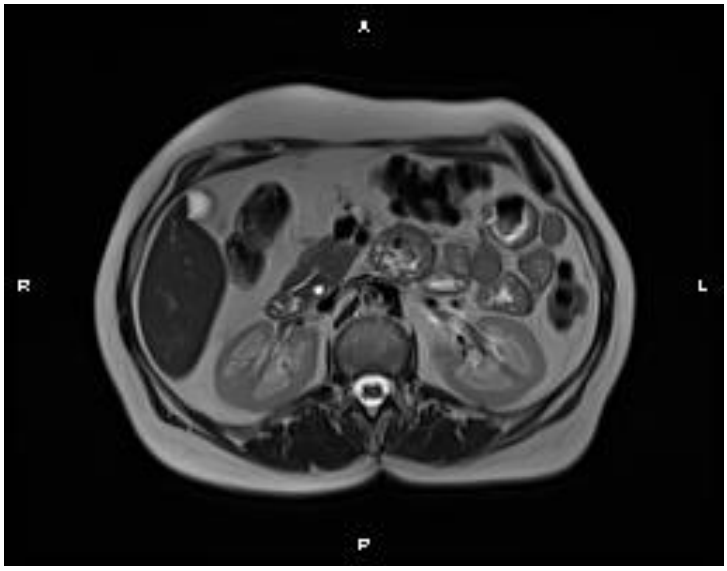


(a)

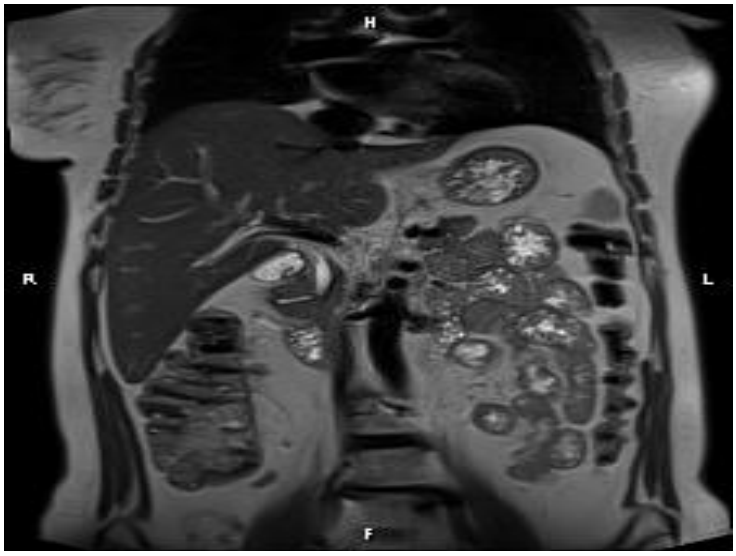


(b)

Figure 1. Axial CT images after iodinated intravenous contrast injection, arterial phase (a) and venous phase (b): Santorini duct opening in the medial wall of the duodenum II through papilla minora, separate from the Wirsung duct - pancreas divisum type I.



(a)



(b)

Figure 2. T2 single shot sequence with short time of echo images, axial plane (a) and coronal plane (b): pancreatic drainage variant with dorsal pancreatic duct, draining in papilla minor, and common bile duct draining in papilla major, without the presence of pancreatic ventral duct - pancreas divisum type II.

CASE REPORT

A 37-year old Caucasian man diagnosed in 2005 with chronic recurrent pancreatitis associated with pancreas divisum, with a history of 25 acute episodes of the condition (the last episode recorded in 2018) and secondary diabetes mellitus from 2008 was hospitalized at the "Prof. N.C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases Bucharest in June 2019 for frequent hypoglycemic episodes. The diagnosis of pancreas divisum and chronic pancreatitis was based on imagistic investigations. Other related medical history includes sfincterectomy, stenting of the main bile duct and cholecystectomy.

The diagnosis of diabetes was established in 2008. At onset, treatment with gliclazide 120 mg/day was initiated. In 2014 the patient was admitted in hospital with elevated glycemic values (> 700 mg/dl, glycated hemoglobin-HbA1c=12%), polyuria, polydipsia. At that time, gliclazide was discontinued and basal bolus insulin therapy was initiated (insulin aspart TID and insulin glargine QD). Due to the severe symptoms, differential

diagnosis was made with autoimmune type 1 diabetes (T1D) and autoantibodies to glutamate acid decarboxylase-GAD were assessed. The value was 5 IE/ml which excluded a diagnosis of T1D or LADA. The patient has a family history of diabetes (father and grandmother), is an active smoker and drinks alcohol in excess.

During the current hospitalization, the patient received specific therapeutic education, including instructions for smoking and alcohol cessation and adjustment of insulin doses.

GENERAL CONSIDERATIONS

Several data suggest that pancreas divisum can induce acute pancreatitis by the following possible mechanism:

- duct anomaly can cause inadequate drainage of pancreatic juice and pain caused by obstruction[5];
- impaired epithelial ion transport might be involved as a triggering factor for acute episodes of pancreatitis through abnormal pancreatic secretion[6].

There is controversy regarding the potential association between pancreas divisum and chronic pancreatitis. Thus, a Japanese cross-sectional study which enrolled 46 patients with idiopathic pancreatitis and 504 control subjects extracted from 70.122 consecutive MRI revealed pancreas divisum could be a significant condition predisposing for recurrent and chronic pancreatitis[7]. In another paper, Takuma K *et al.* reported that chronic pancreatitis occurs more frequently in patients with pancreas divisum than in subjects without this anomaly but the presence of another factor such as alcohol excess may be required for evolution towards chronic pancreatitis[8]. On the other hand, some other studies did not confirm an association of pancreas divisum with pancreatitis. Thus, in an older study, Burtin P *et al.* have analyzed the features of patients with pancreas divisum in order to assess the role of this variation of pancreatic duct anatomy in the occurrence of pancreatitis[9]. The result of the study showed that pancreas divisum cannot be considered as directly involved in the occurrence of pancreatitis[9]. Finally, Bülow R *et al.* in a more recent study (published in 2014) entitled "*Anatomic variants of the pancreatic duct and their clinical relevance: an MR-guided study in the general population*" state that pancreas divisum is not associated with alteration of pancreatic exocrine function and/or morphological changes specific for chronic pancreatitis[10].

Diabetes mellitus is a frequent complication of chronic pancreatitis with prevalence estimates ranging from 20% to 80%[11]. Major diagnostic criteria for diabetes secondary to pancreatic diseases have been proposed in 2013 by Ewald N and Bretzel RG[12]. In addition to classic criteria for diabetes diagnosis, these are represented by exocrine pancreatic insufficiency, pathological pancreatic imaging and the absence of autoimmune markers of type 1 diabetes[12]. Currently there are no international guidelines regarding the treatment of diabetes secondary to pancreatic diseases. The pharmacological agents used for the treatment of this condition are the same as for type 2 diabetes mellitus, with the more frequent requirement for insulin usage due to decreased beta cell mass.

Special considerations for the management of pancreatogenic diabetes could be:

- metformin should be the first line of treatment and in case of therapeutic failure, insulin treatment must be timely added for adequate glucose control[12];
- treatment with insulin and insulin secretagogues might increase the risk of malignancy[13];
- incretin-based therapies could be associated with increased risk of pancreatitis and their use in pancreas divisum should be avoided until their safety is confirmed[12];
- the management of diabetes secondary to pancreatic diseases is characterized by increased susceptibility to frequent episodes of hypoglycemia[14];
- adequate pancreatic enzyme replacement prevents malnutrition and metabolic complications[13].

CONCLUSIONS

Diabetes mellitus is a frequent complication of recurrent and chronic pancreatitis. The management of diabetes secondary to pancreatic diseases requires lifestyle optimization measures (diet, exercise, smoking and alcohol cessation), glucose lowering therapy but also the association of pancreatic enzyme replacement which can prevent denutrition and metabolic complications.

REFERENCES

1. DiMagno MJ, Wamsteker EJ. Pancreas divisum. *Curr Gastroenterol Rep*, 13(2): 150-156, **2011**.

2. Borghei P, Sokhandon F, Shirkhoda A, Morgan DE. Anomalies, anatomic variants, and sources of diagnostic pitfalls in pancreatic imaging. *Radiology,* 266(1): 28–36, **2013**.
3. Kuzel AR, Lodhi MU, Rahim M. Pancreatic Divisum: An Unusal Cause of Chronic Pancreatitis in a Young Patients. *Cureus*, 9(11): e1856. doi: 10.7759/cureus.1856, **2017**.
4. Chalazonitis NA, Lachanis BS, Laspas F, Ptohis N, Tsimitselis G, Tzovara J. Pancreas divisum: magnetic resonance colangiopancreatography fidings. *Singapore Med J*, 49(11):951-4; quiz 955, **2008**.
5. Cotton PB. Congenital anomaly of pancreas divisum as cause of obstructive pain and pancreatitis. *Gut*, 21(2):105–114, **1980**.
6. Dray X, Fajac I, Bienvenu T, Chryssostalis A, Songni P, Hubert D. Association of Pancreas Divisum and Recurrent Acute Pancreatitis with the IVS8-5T-12TG Allele of the CFTR Gene and CFTR Dysfunction. *Pancreas*, 35(1): 90–93, **2007**.
7. Gonoi W, Akai H, Hagiwara K, Akahane M, Hayashi N, Maeda E, Yoshikawa T, Tada M, Uno K, Ohtsu H, Koike K, Ohtomo K. Pancreas divisum as a predisposing factor for chronic and recurrent idiopathic pancreatitis: initial in vivo survey. *Gut*, 60(8): 1103-1108, **2011**.
8. Takuma K, Kamisawa T, Tabata T, Egawa N, Igarashi Y. Pancreatic diseases associated with pancreas divisum. *Dig Surg*, 27(2) :144-148, **2010**.
9. Burtin P, Person B, Charneau J, Boyer J. Pancreas divisum and pancreatitis: a coincidental association? *Endoscopy*, 23(2): 55-58, **1991**.
10. Bülow R, Simon P, Thiel R, Thamm P, Messner P, Lerch MM, Mayerle J, Völzke H, Hosten N, Kühn JP. Anatomic variants of the pancreatic duct and their clinical relevance: an MR-guided study in the general population. *Eur Radiol*, 24(12):3142-3149, **2014**.
11. Hart PA, Bellin MD, Anderson DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, Goodarzi MO, Habtezion A, Korc M, Kudva YC, Pandol SJ, Yadav D, Chari ST, Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC). Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol*, 1(3): 226-237, **2016**.
12. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (Type 3c) - are we neglecting an important disease? *Eur J Intern Med*, 24(3):203–206, **2013**.
13. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. *Pancreatology,* 11(3): 279-294, **2011**.
14. Larsen S. Diabetes mellitus secondary to chronic pancreatitis. *Dan Med Bull*, 40(2): 153–162, **1993**.