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CASE REPORT

Agenesis of the Dorsal Pancreas Presented with Cholestatic Syndrome: Report of Two Cases and Review of Literature

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Abstract

Background: Dorsal agenesis of the pancreas is a rare congenital disorder characterized by the absence of the body, tail and ventrosuperior part of the head of the pancreas. Magnetic Resonance Cholangiopancreatography is the primary diagnostic method to confirm diagnosis, and, in that case pancreatic duct is not visible. Summary: We presented two cases of dorsal pancreatic agenesis associated with cholestatic syndrome. Both cases are young adults with cholestatic type of the liver function tests abnormalities, without symptoms and radiographically confirmed with pancreatic agenesis. Viral markers and autoantibodies suggestive of liver disease were negative, alpha-1 antitrypsin levels were normal, and there were no criteria for the diagnosis of Wilson's disease. Further examination confirmed the presence of an HNF1B mutation in both patients. A literature review revealed two cases where dorsal agenesis of pancreas was associated with cholestatic syndrome, both had mutation of HNF1B. Besides liver disease, such patients are prone to kidney disease and diabetes mellitus.

Key Messages: The aim of the -article is to raise awareness about this rare syndrome, and help identifying this frequently overlooked patient subpopulation.

Keywords: Dorsal Agenesis of the Pancreas, Cholestatic Syndrome, HNF1B Mutation

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Introduction

Dorsal agenesis of the pancreas is a rare congenital disorder characterized by the absence of the dorsal part, specifically the head, as well as the body and tail of the pancreas. The division into ventral and dorsal pancreas is based on embryological development [1]. The primary diagnostic method to confirm the diagnosis, Magnetic Resonance Cholangiopancreatography (MRCP) is required to exclude the presence of a pancreatic duct [2]. Dorsal pancreatic agenesis is often associated with other conditions and diseases, such as diabetes mellitus (DM) and pancreatitis [3]. Interestingly, agenesis is typically diagnosed during the extensive diagnostic work-up of these conditions. We aimed to present two cases of dorsal pancreatic agenesis associated with cholestatic syndrome, with a review of the available literature.

Case A:

A 26-year-old male patient was admitted to the Department of Gastroenterology and Hepatology for the evaluation of liver function tests (LFT) abnormalities. The LFT abnormalities were detected during a routine endocrinology check-up since the patient was treated for DM. The patient has been treated for DM type 1 for the past two years, with a combination of short and longacting insulin analogues. The patient denies other chronic illnesses and mentions having had tonsillectomy in early childhood. The patient reports daily consumption of alcohol and energy drinks. The patient's grandfather had leukemia and there is no other known chronic conditions or diseases in the family. The patient denies any symptoms. The physical examination was unremarkable. Laboratory tests revealed the following abnormalities: AST 27 U/L, ALT 46 U/L, ALP 197 U/L, GGT 106 U/L, total bilirubin 17.7 µmol/L, alpha-amylase 50 U/L, lipase 12 U/L, LDH 202 U/L. The complete blood count showed signs of erythrocytosis (RBC $6.2x10^{12}$/L, Hgb 185 g/L, MCV 82 fL) and mild leukocytosis (WBC $10.1x10^{9}$/L) with neutrophil predominance, and platelets within reference range (PLT $198x10^{9}$/L). Viral serological markers (anti-HIV, anti-HCV, HBsAg, anti-HBc, CMV, and EBV IgM antibodies) and liver specific autoantibodies (ANA, ASMA, AMA, anti-LKM1, ANCA) were negative, while alpha-1 antitrypsin and ceruloplasmin levels were within reference range. HbA1c was 6.0%, which suggested adequate glycoregulation. In urine analyses without proteinuria. Abdominal ultrasound showed normal liver morphology with the exception of slightly prominent intrahepatic bile ducts. The pancreas was only visible at the head region. Further MRCP revealed the absence of the body and tail of the pancreas (Fig.1), with presence of Santorini's duct, a normal biliary tree morphology, and bilateral renal cysts (Bosniak I). A percutaneous liver biopsy was performed, which showed findings consistent with minimal hepatitis at the stage of mild fibrosis, with increased dry mass copper content. However, according to the Leipzig criteria, the patient did not fulfill the diagnostic criteria for Wilson's disease [4]. At discharge the patient was prescribed ursodeoxycholic acid. After hospitalization, clinical exome sequencing (CES) was conducted, which identified the presence of an HNF1B mutation.

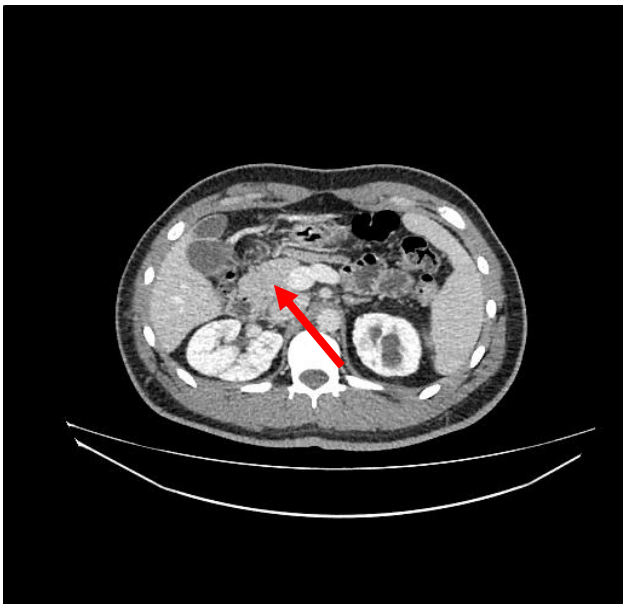

Figure 1: Dorsal agenesis of pancreas (Red arrow-processus uncinatus and head of pancreas)

Case B:

A 25-year-old female patient was admitted to the Department of Gastroenterology and Hepatology, in June 2024, for further evaluation of LFTs abnormalities. On admission the patient reported no complaints. Reports no other conditions or family history of chronic diseases. After careful examination of medical history, it was revealed that the patient's LFT abnormalities were first detected at the age of 12 during routine laboratory testing. Afterward, she was examined at the pediatric department, where imaging showed normal liver presentation, dorsal pancreas agenesis, and bilateral renal cysts. Microdeletion in the 17q12 region, which involves the HNF1B gene was identified after CES was performed. A liver biopsy performed at that time showed no signs of fibrosis. Currently, the laboratory findings are as follows: AST 47 U/L, ALT 55 U/L, ALP 119 U/L, GGT 134 U/L, with normal complete blood count parameters (RBC $4.45x10^{12}$/L, Hgb 134g/L, PLT 320 $x10^{9}$/L, WBC 7.1 $x10^{9}$/L). Synthetic and excretory liver functions are preserved, with INR 0.9, albumin 43 g/L, and total bilirubin 5.0 µmol/L. Normal values of blood glucose and

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urinalysis, The patient did not fulfill the diagnostic criteria for Wilson's disease, and alpha-1 antitrypsin levels were normal (1.44 g/L). Liver specific autoantibodies revealed low titer anti-smooth muscle autoantibodies (ASMA) positivity of 1:80. MRCP confirmed the presence of dorsal pancreatic agenesis, without visualizing of Santorini's duct, bilateral renal cysts (Bosniak I/II), and a normal biliary tree morphology. There were no radiological or endoscopic signs of portal hypertension. Liver stiffness estimated by 2D Shear wave elastography was 5.7 kPa (IQR/Med 28.9%), indicating no liver fibrosis. Since no clinical or laboratory signs of chronic liver disease were detected, the patient was discharged with ursodeoxycholic acid therapy and continued follow-up.

Discussion:

The embryological development of the pancreas begins in the 5th week of gestation, and it involves the separation of the ventral and dorsal buds from the endoderm of the digestive tract, distal to the area where the stomach develops. The ventral bud forms the ventral part of the pancreas, the uncinate process, and the posteroinferior part of the head, while the dorsal bud gives rise to the ventrosuperior part of the head, the neck, body, and tail of the pancreas [1]. Dorsal pancreatic agenesis is a rare disorder, first described in 1911 by Heiberg [5]. Until 2008, 57 cases had been confirmed by Schnedl *et al*, and by 2016, an additional 53 cases were reported [3-5]. Depending on the presence or absence of Santorini's duct, dorsal pancreatic agenesis can further be classified as partial or complete [6]. The increase in newly discovered cases of pancreatic agenesis can be partly explained by the rising availability of radiological methods. Several genes have been identified that may be responsible for dorsal pancreatic agenesis, such as the *PDX1* (insulin promoter factor 1), *HNF1B* (hepatocyte nuclear factor 1 beta), and the *GATA6* (GATA binding factor-6) gene [7]. According to the literature review, the genetic testing, and especially identification of *HNF1B* mutation has been performed in the minority of the reported cases. A search of PubMed database using the keywords ‘dorsal pancreatic agenesis’ and ‘HNF1B’ identified nine articles. In order to diagnose dorsal pancreatic agenesis, it is necessary to perform Endoscopic Retrograde Cholangiopancreatography (ERCP) or MRCP, which would confirm the absence of the mentioned parts of the pancreas and the pancreatic ducts [2]. According to the literature, the most common clinical manifestation of dorsal pancreas agenesis is abdominal pain [8-10]. Abdominal pain can be caused by pancreatitis, Oddi sphincter dysfunction, duodenal obstruction, or some other reason [8]. According to Schnedl et al., 50% of patients have either impaired glucose metabolism or DM [3]. DM is a result of the absence of Langerhans islets, which are predominantly located in the body and tail of the pancreas [1-3,6]. However, both of our patients reported no symptoms, while only one out of two patients had an established diagnosis of DM at the time of dorsal pancreas agenesis diagnosis. Furthermore, both patients presented with similar cholestatic LFT abnormalities pattern, and the diagnosis of dorsal pancreas agenesis was established during the suspected liver disease diagnostic work-up, which differs from clinical presentation of other reported *HNF1B*-associated dorsal pancreas agenesis. It could be assumed that the exact *HNF1B* gene mutation most likely links dorsal pancreas agenesis with cholestatic syndrome in the two presented cases. The mutation of *HNF1B* gene and the subsequent deficiency of the gene product are also associated with the renal cyst syndrome and DM in young individuals (typeMODY5), as reported by Kotalova et al. [11]. In this case, genetic mutation causes a dysfunction of insulin secretion, and DM typically develops by the age of 25 [11]. Interestingly, Roelandt et al. identified ciliary anomalies in cholangiocytes, which may be the cause of cholestasis in patients with *HNF1B* mutation [12]. Kotalova et al. studied 12 patients of different ages with elevated liver enzymes associated with the *HNF1B* mutation [11]. Cholestasis wasdescribed in eight cases. In four patients, the complete absence of the body and tail of the pancreas was described, while pancreas atrophy was detected in two cases. Among all these cases, the simultaneous existence of dorsal pancreatic agenesis and cholestasis has been described in two cases (Table 1). Based on age and pathohistological findings, several types of hepatic phenotypes of *HNF1B* mutation were described. The most severe, neonatal cholestasis form is characterized by varying levels of fibrosis in the portal spaces, and the development of diabetes within the first two decades of life, along with renal cysts and early onset of renal insufficiency. Cognitive developmental delay is also described within this syndrome. The intermediate type occurs when cholestasis appears between the ages of 29-44, with milder changes in liver histology, such as sinusoidal dilation. In this subgroup, DM occurs between 14 and 51 years of life, and chronic renal insufficiency occurs later than in previous subgroup of patients. Therefore, the presented two cases would most likely fit into the described intermediate type of cholestatic syndrome. However, the more advanced liver histology reported in case A could be the result of several underlying mechanisms including the genetic syndrome phenotype, alcohol and energy drinks consumption, as well as poor glycoregulation. The last, and mildest form of the syndrome, includes asymptomatic patients with elevated liver enzymes without cholestasis [11,13].

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Table 1: Dorsal agenesis of pancreas associated with cholestasis and HNF1B mutation

Ref.	Sex/Age	Symptoms	Laboratory	Liver biopsy	Associated diseases and findings
[13]	Male/At birth	Laboratory findings at birth	GGT 213IU/L (<28)	Slight periportal fibrosis	Neonatal hyperglycemia and diabetes at 5y; Renal cysts
[10]	Female/At birth	jaundice	GGT 1398 IU/L, total bilirubin 104 µmol/L	Dilated portal fields, periportal fibrosis, thin atretic bile ducts	Renal cysts
Present case A	Male/26	Asymptomatic/Laboratory finding	ALP 197 U/L, GGT 106 U/L	Mild fibrosis	Diabetes at 24y; Renal cysts
Present case B	Female/12	Asymptomatic/Laboratory finding	GGT 134 U/L, AST 47 U/L, ALT 55 U/L, ALP 119 U/L	No signs of fibrosis	Renal cysts

Conclusion:

Dorsal agenesis of the pancreas is a rare developmental disorder of the pancreas characterized by the absence of the ventrosuperior part of the head of the pancreas, as well as the body and tail. The most common clinical manifestation is abdominal pain, although patients often do not have any symptoms, when in such cases disorder is discovered during the investigation of associated diseases and conditions, such as cholestatic syndrome. Several types of cholestatic syndrome associated with dorsal agenesis of pancreas have been described, based on the age at which the disorder manifests and the severity of liver histology. It appears that cholestatic syndrome and dorsal agenesis of the pancreas most commonly co-exist as a result of the mutation in the *HNF1B* gene. However, given the small number of cases, further investigation of this rare syndrome is needed in order to identify undiagnosed patients, optimal treatment methods, and disease prognosis.

Ethics Statement

Written informed consent has been obtained from the patients.

Conflicts of Interest Statement

The authors declare no conflict of interest.

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This research received no external funding.

Author contributions

NB primary author, completed the review of the literature. IP, IV, MV participated in data collection, patients work-ups and manuscript editing. TM supervisor in the diagnosis and treatment of patients, ideas for manuscript, edited manuscript. MS radiological image interpretation.

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