Congenital Pancreatic Hypoplasia Associated with Paucity of Bile Ducts and Renal Microcysts in an Arab Israeli Family

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Congenital pancreatic hypoplasia, which affects exocrine and endocrine pancreatic functions, is a rare syndrome that causes early-onset insulin-dependent diabetes mellitus and malabsorbtion, leading to failure to thrive. It is associated with high morbidity and mortality in affected infants [1]. We report the cases of two related female infants with congenital pancreatic hypoplasia conjoint with paucity of intrahepatic bile ducts and renal cortical microcysts.

Patient Descriptions

Patient 1

Patient 1 was the seventh child of consanguineous first cousins. Both parents were healthy and of Muslim origin. No pregnancy follow-up was performed until 31 weeks of gestation, at which time an elective cesarean section was carried out due to severe intrauterine growth retardation. An initial physical examination revealed a severely malnourished female infant. Birth weight, length and head circumference were all below the 3rd percentile. Persistent hyperglycemia (>250 mg/dl) was observed soon after birth with undetectable serum insulin. Insulin treatment was therefore initiated. On the second day of life, abdominal distension and jaundice developed, followed by foamy green stools that gradually changed to acholic stools and intermittent emesis without weight gain. Laboratory evaluation revealed conjugated hyperbilirubinemia and elevated liver enzymes, with maximal values of 12 mg/dl and 20 mg/dl of direct bilirubin and indirect bilirubin, respectively. Anti-insulin and anti-islet cell antibody levels were undetectable in the maternal blood. Qualitative stool examination revealed an increased amount of natural fat, glucose and other reducing substances. Elastase-1 levels in stool were 0 (normal $\geqslant$ 200 μg/g), and serum lipase and amylase levels were undetectable. Metabolic studies were normal except for high levels of glycine, methionine and lactate in the urine, which was related to hepatic failure. Viral studies were negative. Eye examination and echocardiography were normal, as was abdominal ultrasound, however abdominal computed tomography scan showed an atrophic pancreas, with only part of the head of the pancreas visible, and no other abnormality. Karyotype revealed 46XX normal cell line. Mutations commonly associated with cystic fibrosis in Israeli Arabs (ΔF508, N1303K, 3120+1Kbdel18.6Kb, W1282X, G85E, 2183AA>G) were not identified. Although pancreatic enzyme replacement therapy (pancreatin) and an elementary diet (neocate-amino acids-fat-minerals compound) were introduced, no weight gain was achieved. At 3.5 months, the infant died of *Escherichia coli* sepsis, severe failure to thrive and hepatic failure.

Patient 2

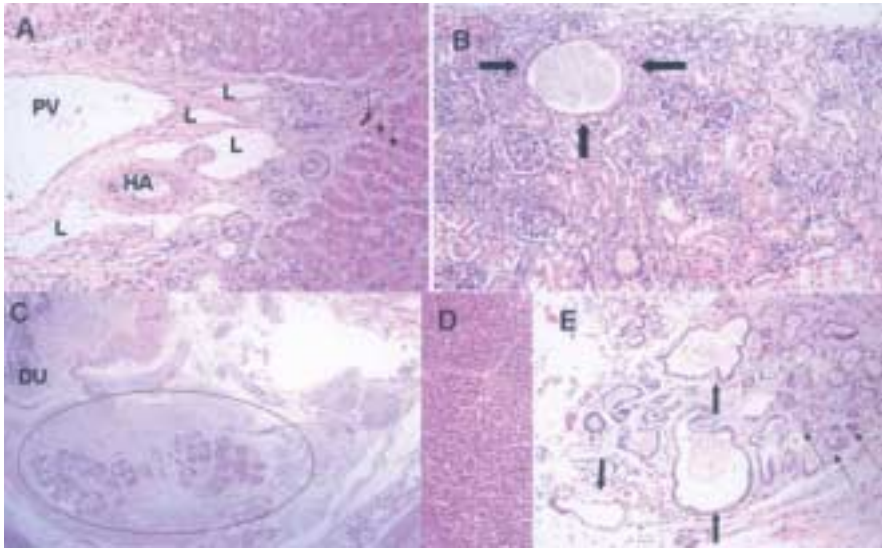
Patient 2 was a female, term infant, who was the niece of patient 1. Birth weight, head circumference and length were all below the 3rd percentile. Early IDDM, severe malabsorbtion, and cholestatic jaundice were observed. Insulin levels were undetectable and the level of elastase 1-trypsin in stool was measured as 0. Karyotype was 46XX. Detection of uniparental disomy of chromosome 6, as described in cases of congenital diabetes mellitus, proved negative. Although aggressive treatment with insulin and pancreatic enzymes was initiated, the infant did not gain weight and died at 4 months of age from hepatic failure.

Autopsy findings revealed severe paucity of intrahepatic bile ducts with bile stasis and periportal fibrosis with occasional portoportal bridging but no cirrhosis, severe pancreatic hypoplasia with absence of endocrine islets, and atrophy of exocrine pancreas associated with fibrosis and hemosiderin deposits. Normal architectural landmarks were identifiable in both kidneys. Histologically, there were numerous microcysts, surrounded by normal-looking glomeruli and tubules with no cortical dyplasia or fibrosis [Figure].

Comment

The pathologic hallmarks of our two patients were pancreatic hypoplasia and paucity of intrahepatic bile ducts, with renal microcysts. Currently, there are few reports of these diseases involving these organs. Ivemark et al. [2], among others [3], described a combination of abnormalities, which they named "renal-hepatic-pancreatic dysplasia" sequence. In our patients no renal dysfunction or dysplasia was evident

IDDM = insulin-dependent diabetes mellitus



Histologic autopsy findings in patient 2. **[A]** Liver with a large portal vein (PV), hepatic artery (HA) with small arterial branches (circles), dilated lymphatics (L), bile plugs (arrows). No evidence of bile ducts (hematoxylin & eosin, x 40). **[B]** Kidney: cortical microcyst (arrows) surrounded by normal appearing glomeruli and tubules (H&E, x 40). **[C]** Remnant of pancreas surrounded by fibrosis (ellipse), adjacent to duodenum (DU) (H&E, x 10). **[D]** Pancreas of an age-matched baby: confluent densely arranged pancreatic lobules (H&E, x 20). **[E]** Lobule of pancreas: a few atrophic exocrine acini (thin arrows), distorted dilated ductules with irregular outlines (thick arrows). No Langerhans islets (H&E, x 20).

as only microcysts were demonstrated, while the pancreatic abnormality consisted mainly of hypoplasia and no dysplasia. However, the RHPD sequence has shown considerable variability in histologic and clinical findings, which may reflect the varying phenotype of a single gene condition. Renal-hepatic and pancreatic dysplasia may well be a component of various syndromes, such as polycystic disease, Saldino-Noonan syndrome, trisomy 9 or type II glutaric aciduria, but these were excluded in our patients who had normal phenotype and genotype and negative metabolic screen. There was some resemblance in our patients to partial Alagille syndrome, such as cholestasis with paucity of bile ducts, a kidney with sub-cortical cysts and IDDM; however, patients with partial Alagille syndrome usually survive the neonatal period and have characteristic facial features that were absent in our patients. Few key genes in pancreatic development have been identified that could theoretically be the etiology for pancreatic hypoplasia [4]. A study of a patient with complete pancreatic agenesis showed homozygosity for a non-sense mutation in the *IPF1* (insulin promoter factor) gene [5]. However, no other organ malformations were noticed in this patient, unlike our patients.

In summary, we have described two related term infants of Arab Israeli origin, both of whom suffered from pancreatic hypoplasia, paucity of bile ducts and renal microcysts, which eventually led to their deaths. Future understanding of their genetic origin may explain the variable phenotype and may lead to prenatal diagnosis.

RHPD = renal-hepatic-pancreatic dysplasia

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