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ORIGINAL PAPER

Caroli disease, bilateral diffuse cystic renal dysplasia, situs inversus, postaxial polydactyly, and preauricular fistulas: a ciliopathy caused by a homozygous *NPHP3* mutation

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Abstract We report the rare association of Caroli disease (intrahepatic bile duct ectasia associated with congenital hepatic fibrosis), bilateral cystic renal dysplasia, situs inversus, postaxial polydactyly, and preauricular fistulas in a female child. She presented with end-stage renal disease at the age of 1 month, followed by a rapidly progressing hepatic fibrosis and dilatation of the intrahepatic bile ducts, leading to secondary biliary cirrhosis and portal hypertension. Combined liver–kidney transplantation was performed at the age of 4 years, with excellent outcome. DNA analysis showed a *NPHP3* (coding nephrocystin-3) homozygote mutation, confirming that this malformation complex is a ciliopathy. *Conclusion:* This rare association required an exceptional therapeutic approach: combined simultaneous orthotopic liver and kidney transplantation in a situs inversus recipient. The long-term follow-up was excellent with a very good evolution of the renal and hepatic grafts and normalization of growth and weight. This malformation complex has an autosomal recessive inheritance with a 25% recurrence risk in each pregnancy.

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Keywords Caroli disease · Cystic renal dysplasia · Ciliopathy · Combined liver–kidney transplantation

Introduction

Caroli disease is a rare congenital disease that consists of intrahepatic bile duct ectasia associated with congenital hepatic fibrosis [7]. Inheritance is autosomal recessive. Renal anomalies, such as multicystic or polycystic kidney disease, are frequently present as a concomitant finding [8]. We describe in detail a female patient (previously briefly reported under Family 960 in summary Table 1 in [4]) with Caroli disease, bilateral cystic renal dysplasia, situs inversus, postaxial polydactyly, and preauricular fistulas. This very malformation complex has not been reported previously. The management, consisting of combined liver–kidney transplantation, is discussed.

Case presentation

A now 12-year-old girl was born with postaxial left foot polydactyly and bilateral preauricular fistulas. She was diagnosed with rapidly progressive renal failure at the age of 1 month. Her healthy Vietnamese non-consanguineous parents had no known family history of hepatic or renal disease. Peritoneal dialysis was required at 3 months. Renal biopsy showed cystic dilatation of both glomeruli and tubules, with a rim of actin-reactive smooth muscle cells surrounding the dilated structures. Liver biopsy revealed portal fibrosis and interlobular bile duct dystrophy and slight dilatation of bile ducts. At the age of 4 months, the patient needed a gastrostomy for nutritional support. The supernumerary toe was surgically removed at the age of 1 year. At the beginning of her second year of life, the girl was diagnosed with portal hypertension. A further liver biopsy showed extensive fibrosis with interlobular bile duct dilatations, consistent with congenital hepatic fibrosis. At the age of 3 years, the patient had failure to thrive with weight at −2 SD and height at −4 SD. Hepatomegaly (4 cm) in the left upper abdomen and splenomegaly (8 cm) in the right abdomen were noted. Laboratory studies revealed hemoglobin of 102 g/l, a leukocyte count of 9.2×10^3/μl, and a platelet count of 128,000/μl. The liver was functional with a PT >100%, PTT 35.8 s, factor V >100%, factor VII–X >100%, AST 44 U/l, ALT 35 U/l, γGT 118 U/l, AP 416 U/l, LDH 221 U/l, bilirubin 9 μg/l, and albumin 33 g/l. The clinical picture was complicated by stage II esophageal varices. These findings—congenital hepatic fibrosis with multiple segmental cystic dilatations of the intrahepatic bile ducts associated with portal hypertension—thus defined Caroli disease [5, 7]. In addition, a complete situs inversus was diagnosed and confirmed by arteriography and cavography. No anomalies were found in the heart, lungs, and pancreas. The girl showed no intellectual deficiency.

Abdominal CT scan and cholangio-MRI confirmed the abdominal situs inversus and showed an enlarged liver with polycyclic borders and multiple cystic lesions in the right and left hepatic lobes with a saccular enlargement of the main bile duct in the hepatic hilum, as well as esophageal varices and an enlarged multilobulated spleen. The kidneys presented with multiple cysts (2–20 mm). The right hepatic artery originated from the celiac trunk and the gastric artery started off from the left hepatic artery; the portal vein was permeable and of normal size and route (Fig. 1). The voiding cystourethrogram showed a reduced bladder capacity (5 ml) without signs of bladder trabeculation or hypertrophy and a bilateral vesicoureteral reflux of stage II.

Clinical, laboratory, imaging, and histological findings concluded to Caroli disease, bilateral diffuse cystic renal dysplasia, and situs inversus. Given the association with the postaxial polydactyly, a ciliopathy [2] was suspected and DNA was analyzed; sequencing showed a homozy-

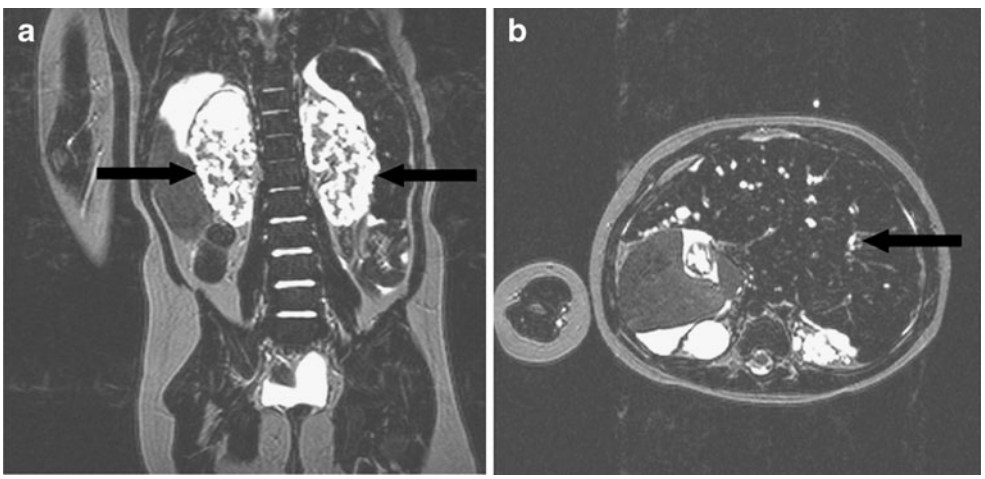

Fig. 1 **a** The abdominal MRI shows the small kidneys with multiple cysts of 2 to 20 mm visible in the T2 sequences (*arrows*) **b** MRI confirms the abdominal situs inversus with an enlarged left-sided liver with polycyclic borders and multiple cystic lesions (*arrow*) in the right and left hepatic lobes

gous mutation in the donor splice site of intron 13 of the NPHP3 gene c. 1985+5G>A, which has been independently shown to be pathogenic [4], thus confirming the hypothesis.

After standard pre-transplantation investigations, the patient was accepted on the waiting list for combined liver–kidney transplantation. One year thereafter, with a weight of 12.9 kg, at the age of 4 years, the patient was liver–kidney transplanted with segments I–IV of a reduced liver and left kidney from one and the same deceased donor. Before implantation of the liver graft, a left nephrectomy was performed. Histological examination of the kidney and liver explants confirmed the diagnostic hypothesis (Fig. 2). Small- to middle-sized cysts were visible on the kidney explant. Histology confirmed the previous biopsy findings of multiple cystic dilatations of the glomeruli and tubules, cuffed by a rim of smooth muscle cells, and interstitial fibrosis. Persistence of fetal glomeruli and multifocal nephrogenic rests were observed in the kidney explant. Nephrogenic rests have been described in the patient with end-stage kidney disease requiring peritoneal dialysis [13]. Fibrous bands of varying width extending between portal tracts with architectural modifications and focal nodule formation were seen on the liver explant. Portal tracts show focally dilated and angulated bile ducts, with ductular reaction, while segmental bile ducts in segment II were more severely dilated.

There were no postoperative graft complications. Eight years after transplantation, at the age of 12 years, the girl is asymptomatic, with good liver and kidney function, and normal weight (35.8 kg) and height (142 cm).

Discussion

Caroli disease is a rare disorder of the intrahepatic bile ducts characterized by multiple saccular segmental, cystic dilatations, and has an incidence of 1/1,000,000 births [17]. The polycystic dilatations are either diffuse throughout the liver or confined to only one of its part [10]. There are two distinct types of the disease: (1) the pure form of Caroli disease and (2) the association of the bile duct dilatations with congenital hepatic fibrosis, leading to portal hypertension in 25% to 50% of cases, which is termed by some authors as Caroli syndrome [27]. The pathogenesis of Caroli disease seems to be related to a ductal plate malformation. Its inheritance is considered to be autosomal recessive, as already shown in some cases in which homozygous mutations of the PKHD1 gene were found [20].

The clinical picture may be complicated by hematemesis and melena due to portal hypertension, hypersplenism, and esophageal varices, as well as hepatolithiasis and gallbladder stones, cholangitis, and intrahepatic abscess formation [27]. Infectious pathogens may become resistant to the antibiotic therapy leading to lethal sepsis or secondary biliary cirrhosis. The chronic inflammation of the biliary tree explains the potential development towards cholangiocarcinoma reported in 7% of patients [9].

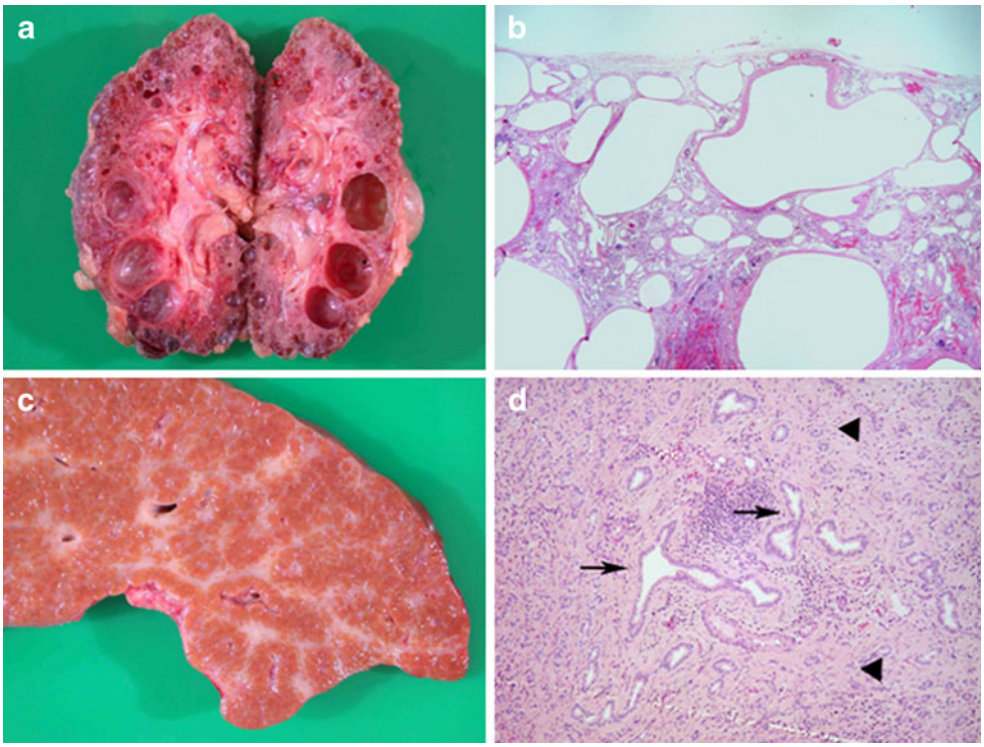

Fig. 2 Diffuse cystic renal dysplasia and congenital hepatic fibrosis. **a** Cut section of the left kidney explant displaying a nodular and irregular surface, and numerous cystic spaces measuring up to 2.2 cm. Corticomedullary differentiation is lost. **b** Histology shows severe architectural disruption and multiple rounded cysts originating from both glomeruli and tubules in the subcapsular region (Hematoxylin & Eosin (H & E), ×20). **c** Upon gross examination, the liver explant shows fibrous bands, with heterogeneous distribution. **d** Microscopic evaluation showing dilated and angulated bile ducts (*arrows*), and ductular reaction (*arrowheads*) (H & E, ×100)

Definitive treatment of Caroli disease is limited: asymptomatic patients need regular follow-up to detect possible deteriorations and malignant transformation; symptomatic patients on the other hand should undergo conservative treatment to stabilize acute cholangitis, necessitating an interventional attempt with a drainage procedure to temporarily improve bile drainage. This may nevertheless become eventually inefficient due to the progression of the disease. Lobectomy relieves the symptoms when one lobe is affected; yet, when the disease is diffuse, liver transplantation is the only treatment that provides good long-term results [5]. Portal hypertension associated with acute variceal hemorrhage needs standard medical and/or endoscopic treatment and ultimately may benefit from a portacaval shunt. In our patient, in the presence of diffuse Caroli disease with an increased risk of cholangitis, choledocholithiasis, and cholangiocarcinoma, which is further enhanced under immunosuppression, liver transplantation was felt to be indicated.

Primary bilateral diffuse cystic renal dysplasia is a rare disorder with an incidence of 1/10,000 births [25]. A chromosomal defect is present in 10% of patients with dysplastic kidneys. In almost all patients, there is another extra-renal anomaly such as pulmonary hypoplasia, secondary to the concomitant oligohydramnios, and a strong correlation with vesicoureteral reflux [15]. Such a dysplasia is often also a component of syndromes such as Bardet–Biedl, Beckwith–Wiedemann, branchio-oto-renal, DiGeorge, Meckel–Gruber, or CHARGE [26]. It usually has a very poor prognosis: infants with severe disease often die in the neonatal period secondary to a combination of pulmonary hypoplasia and renal failure; in the absence of respiratory failure, peritoneal dialysis is possible even in infants with low weight [27]. Survivors represent the most frequent cause of chronic renal failure in early childhood, accounting for 25% of children requiring renal transplantation [26].

About 60–80% of patients with Caroli disease have associated renal lesions varying from tubular ectasia to multicystic or polycystic kidney disease [24]. The association of Caroli disease with autosomal recessive polycystic disease is quite commonly reported [23], whereas the combination with autosomal dominant polycystic kidney disease is reported only in four cases in the English literature [22]. Our patient had bilateral cystic renal dysplasia.

The reported girl presented with chronic anuric renal failure, treated by peritoneal dialysis from the age of 3 months, and required renal transplantation. She had no pulmonary abnormalities. At the time of transplantation, unilateral renal nephrectomy was performed since poor prognosis is reported if bilateral renal nephrectomy and kidney grafting are done at the same time [11].

As there was clear indication for kidney transplantation in our patient, the choice lied between simultaneous liver–kidney transplantation, sequential liver after kidney transplantation or vice versa. The benefit of combined transplantation has been demonstrated in the cases of Caroli disease associated with renal polycystic disease [18]. The rather important immunosuppression after kidney transplantation may contribute to the later development of cholangitis or cholangiocarcinoma; thus, if the two diseases progress concomitantly, simultaneous liver–kidney transplantation is suggested [21]. The high incidence of complications and recurrent symptoms after conservative treatments of Caroli disease (liver resection, fenestration, different endoscopic procedures) also recommend combined transplantation as a rather safe therapy. Delay of transplantation results in more difficult surgical techniques, increased rates of postoperative complications, and difficulties in optimal transplantation because of the worse preoperative condition of patients [5].

With an incidence of 1/8,000–1/25,000 live births, situs inversus is a rare anomaly in which a mirror image reversal of the usual organ arrangement occurs. Eighty percent of the patients are affected by other congenital anomalies, such as heart malformations, ciliary dyskinesia [1, 8], congenital hepatic fibrosis [19], intrahepatic biliary dysgenesis in the larger context of pancreatic fibrosis, and/or renal pathologies such as bilateral renal cystic disease [12], autosomal recessive polycystic kidney disease [14], or renal cystic disease [6, 16].

The liver pathology associated with situs inversus may require liver transplantation. The technical aspects of liver transplantation in these patients are more challenging than simply overcoming the mirror image of the liver anatomy. The complex vascular anomalies associated with situs inversus increase the technical difficulties of the liver transplantation and may result in a high complication rate in these patients, especially in the context of an interrupted inferior vena cava, a preduodenal portal vein, and an anomalous hepatic artery origin. As the arteriography and cavography did not show major vascular anomalies in our patient, she therefore benefited from orthotopic reduced-liver transplantation into the left hemiabdomen.

As far as etiology is concerned, the combination of signs observed in the present case led to the hypothesis that it could be part of the recently delineated spectrum of conditions known as ciliopathies. The finding of a homozygous mutation in the NPHP gene proved that the assumption was correct and confirmed that the syndrome we report follows autosomal recessive inheritance with a 25% recurrence risk in each pregnancy. A thorough review on ciliopathies is published in this issue by Bergman et al. [3].

Consent

Written informed consent was obtained from the patient's family for publication of this case report and accompanying

images. A copy of the written consent is available for review by the editor-in-chief of this journal.

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Competing interests The authors declare that they do not have any competing interests.

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