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ORIGINAL PAPER

Abnormalities of the biliary tract in patients with autosomal recessive polycystic kidney disease (ARPKD)

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ABSTRACT

Introduction: Autosomal recessive polycystic kidney disease (ARPKD) is a ciliopathy with kidney and liver manifestations. Children with ARPKD usually remain only under the care of nephrologist due to silent liver involvement characterized by congenital hepatic fibrosis with or without bile ducts dilatation. The aim of this study is to pay attention on the occurrence of the abnormalities of the biliary tract in ARPKD patients.

Material and methods: Data on laboratory (serum total and direct bilirubin concentration, gamma-glutamyltranspeptidase [GGT] activity, serum bile acids concentration) and imaging examinations findings (intrahepatic and extrahepatic bile ducts dilatation, biliary cysts), as well as data on history of cholangitis, were analysed retrospectively in 17 patients (14 male and 3 female, aged from 2.5 to 42 years) with molecularly confirmed diagnosis of autosomal recessive polycystic kidney disease (ARPKD).

Results: Increased GGT activity was noticed in 7 patients and slightly increased direct bilirubin in 8 (46.7 and 53.3% respectively). Only one patient had a history of cholangitis. Dilatation of intrahepatic bile ducts and common bile duct on ultrasound examination was described in 10 and 5 patients respectively. There was no close correlation between laboratory and imaging examination findings. Four our patients with dilated bile ducts had normal laboratory results, while two patients had abnormalities only in laboratory tests. Both, laboratory and imaging abnormalities were found in 6 and none of them in 5 patients.

Conclusions: In patients with ARPKD abnormalities of the biliary tract can occur even when standard laboratory tests findings stay within normal limits. Detailed biliary tree imaging evaluation should be performed in each patients with increased GGT activity/bile acid concentration, history of cholangitis, before kidney transplantation, as well as in adolescents and young adults due to increased risk of cholangiocarcinoma.

KEY WORDS:

cholestasis, congenital hepatic fibrosis, Caroli syndrome, autosomal recessive polycystic kidney disease.

INTRODUCTION

Autosomal recessive polycystic kidney disease (ARPKD) occurs in approximately 1 in 20,000 children, what makes it the most common ciliopathy of childhood. ARPKD is typically characterized by cystic dilatation of the renal collecting tubules and congenital hepatic fibrosis with or without dilatation of the bile ducts.

Embryogenesis of the biliary system commences in the first weeks of gestation and lasts until 28th week [1]. Between 12th and 20th week this process relies on remodelling and partial involution of the ductal plate (cylindrical layer of cells that surrounds a branch of the portal vein).

Insufficient remodelling and resorption due to defects in the primary cilia of cholangiocytes leads to ductal plate malformation (DPM).

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DPM results, depending on the timing or stage of development, in a spectrum of abnormalities including:

- multiple hamartomas or biliary microhamartomas (Von Meyenburg complexes, VMC) – the failure of involution of embryonic bile ducts;
- congenital hepatic fibrosis (CHF) – the failure of microscopic bile ducts involution;
- Caroli syndrome (CS; Caroli disease in association with CHF) – the failure of involution of microscopic and medium size bile ducts;
- Caroli disease (CD) – the failure of involution of medium and large bile ducts;
- isolated liver cysts in polycystic liver disease (PCLD) – result of malformation of the embryonic ductal plate with formation of von Meyenburg complexes lined with functional biliary epithelium [2–5].

It is worth emphasizing, that more than one form of DPMs can coexist in the same patients [2].

The congenital hepatic fibrosis and Caroli syndrome are the most frequent liver pathology in ARPKD.

The clinical course and dynamics of portal hypertension due to congenital hepatic fibrosis in our ARPKD cohort was described previously (report submitted for publication in Frontiers in Pediatrics). In this paper we describe biliary tract abnormalities and discuss its consequences in ARPKD patients. The aim of this study is to pay attention on the occurrence of the abnormalities of the biliary tract in ARPKD patients.

MATERIAL AND METHODS

This study includes patients with molecularly confirmed diagnosis of ARPKD, who are/were treated in The Children's Memorial Health Institute in Warsaw.

We analysed retrospectively:

- laboratory findings: serum total and direct bilirubin, gamma-glutamyltranspeptidase (GGT), serum bile acids;
- ultrasound features: intrahepatic and extrahepatic bile ducts dilatation (normal values for common bile duct were based on criteria described by Lindholm *et al.* [6]: normal sized common bile duct < 1.8 mm for patients < 1 year old; < 2.7 mm for patients between 1 and 10 years old; < 4.2 mm for patients > 10 years of age), biliary cysts;
- liver scintigraphy;
- magnetic resonance cholangiopancreatography (MRCP);
- abdominal computed tomography (CT);
- history of cholangitis.

The study protocol was approved by the Children's Memorial Health Institute Bioethical Committee, Warsaw, Poland. An informed consent was obtained from all the involved participants.

RESULTS

The study group consists of 17 patients (14 male and 3 female) with ARPKD confirmed by molecular test. The patient's age ranges from 2.5 to 42 years (median: 15 years).

One patient (P2) died at the age of 29 months. In the remaining group of patients the mean follow-up time after the initial diagnosis was 14 years (6–37 years).

One patient (P9) underwent kidney transplantation (KTx) at the age of 3 and another (P10) combined kidney/liver transplantation (CKLTx) at the age of 37 years.

Laboratory and imaging characteristics of our patients is presented in Table 1.

Increased GGT activity was noticed at least once in 7/15 (46.7%) patients (two patients [P10, P14] were excluded from the analysis due to incomplete data on GGT activity from adult discharge follow-up), first time at the age of 1–13 years (median: 6 years). In all but one GGT activity measurements were < 100 IU/l. P4 has an episode of GGT elevation up to 467 IU/l with coexisting hypertransaminasemia (aspartate transaminase [AST]: 113 UI/l, alanine transaminase [ALT]: 130 UI/l) but total bilirubin within normal value.

Slightly increased direct bilirubin (0.21–0.33 mg/dl) with normal total bilirubin was detected in 8 patients, first time at the age of 3–14 years (median: 7.5 years). Only in one of these patients (P6) GGT activity was within normal limits.

Results of bile acids concentration were available only in 3 patients (P1, P3 and P8) and it was above the upper limit of normal in all of them. In patients with elevated biliary acids concentration GGT and direct bilirubin were abnormal.

Dilatation of bile ducts on ultrasound examination was described in 10/16 patients (62.5%) (in one patient [P14] the data on ultrasound examination were inaccessible), first time at the age of 1–11 years (median: 7 years). Common bile duct (CBD) was dilated in 5 patients, first time at the age of 1–12 years (median: 5 years). In remaining patients there were no data on CBD size.

Liver scintigraphy was performed in 4 patients. In 3 of them (P10, P14 and P16) left liver lobe was enlarged. In one patient (P8) latent parenchymal transit of bile was described and dilated bile ducts and slightly lower bile passage to the intestines in other (P16). Uneven marker accumulation suggesting liver cyst was noticed in P10.

Only 2 patients in our cohort (P8, P16) had MRCP. In P8 segmental intrahepatic and extrahepatic bile duct widening and liver fibrosis were described, in P16 – cystic dilation of CBD, dilation of hepatic ducts and slightly dilated intrahepatic ducts with segmental widening.

Abdominal computed tomography was performed in 4 patients and showed dilated bile ducts in P3, hepatosplenomegaly in P12, few, tiny liver cysts in P14 and no pathologic findings in first year of life in P11.

Only P14 has a history of cholangitis at the age of 31 years.

DISCUSSION

In addition to congenital hepatic fibrosis resulting in portal hypertension, biliary tract dilatation is other im-

TABLE 1. Laboratory and imaging characteristics

Patient	Laboratory findings	Imaging examinations findings
P1	Elevated: GGT activity, direct bilirubin and bile acids concentration	Dilated CBD and intrahepatic bile ducts (US)
P2	Results within normal limits	Dilated intrahepatic bile ducts, suspicion of liver cysts (US)
P3	Elevated: GGT activity, direct bilirubin and bile acids concentration	Dilated CBD and intrahepatic bile ducts (US), dilated bile ducts (CT)
P4	Elevated: GGT activity and direct bilirubin concentration	Dilated intrahepatic bile ducts (US)
P5	Elevated: GGT activity and direct bilirubin concentration	No pathologic findings (US)
P6	Elevated: direct bilirubin concentration	Dilated intrahepatic bile ducts, liver cysts (US)
P7	Results within normal limits	Dilated CBD and intrahepatic bile ducts (US)
P8	Elevated: GGT activity and direct bilirubin and bile acids concentration	Dilated CBD and intrahepatic bile ducts, liver cysts (US); latent parenchymal transit of bile (sct); Caroli syndrome (MRCP)
P9	Results within normal limits	No pathologic findings (US)
P10	Results within normal limits*	Dilated intrahepatic bile ducts, liver cyst (US); enlarged left liver lobe, suspicion of liver cysts (sct)
P11	Elevated: GGT activity and direct bilirubin concentration	Dilated intrahepatic bile ducts (US); no pathologic findings (CT)
P12	Results within normal limits	Hepatosplenomegaly (CT)
P13	Results within normal limits	No pathologic findings (US)
P14	Results within normal limits*	Enlarged left liver lobe (sct); few liver cysts (CT)
P15	Elevated: GGT activity and direct bilirubin concentration	No pathologic findings (US)
P16	Results within normal limits	Dilated CBD and intrahepatic bile ducts (US); enlarged left liver lobe, dilated bile ducts, slower bile passage to the intestines (sct); cystic dilatation of bile ducts, liver cysts (MRCP)
P17	Results within normal limits	Liver cysts (US)

*CBD – common bile duct, CT – computed tomography, GGT – gammaglutamyl transpeptidase, MRCP – magnetic resonance cholangiopancreatography, sct – scintigraphy, US – abdominal ultrasound, *incomplete data from adult discharge follow-up*

portant clinical aspect of ARPKD. Bile stagnation in dilated bile ducts puts the patients at risk of cholangitis, hepatic abscess and sepsis as well as cholelithiasis. Chronic inflammation of the biliary tree may results in cholangiocarcinoma [7, 8].

It is known that most ARPKD patients have well preserved hepatocyte synthetic function. Detailed data on biliary tract-related laboratory findings are scarce.

The abnormalities in microscopic and medium size bile ducts in Caroli syndrome may result in cholestasis even in patients without cholangitis [8].

In cholestatic jaundice in infants, the cholestasis is diagnosed when direct bilirubin concentration exceed 1 mg/dl [9]. In other cases (e.g. progressive familial intrahepatic cholestasis, Alagille syndrome) cholestasis can be diagnosed in patients with elevated GGT activity and/or bile acid concentration without hyperbilirubinemia [10–12].

According to this definition, cholestasis occurred in 7 out of 17 our patients.

Compared to other studies, elevation of GGT activity in our group was seen even more frequently (46.7% vs. 13.7 and 38%) [10, 14]. We ruled out drugs (phenobarbital, anticonvulsants) and alcohol intake as the cause of abnormal GGT activity.

There were no reports on elevation of direct bilirubin concentration. Total bilirubin was abnormal in 9.6% of patients presented by Gunay-Aygun *et al.* [10] and in 12% of cohort reported by Burgmaier *et al.* [14].

Imaging examinations findings did not always correlate to laboratory findings. Four our patients with dilated bile ducts had normal laboratory results, while two patients had abnormalities only in laboratory tests. Both, laboratory and imaging abnormalities were found in 6 and none of them in 5 patients. Gunay-Aygun *et al.* had similar observations: of the 10 patients with elevated GGT levels 2 had a normal biliary system; of the 11 patients with biliary cysts only 2 had mildly elevated GGT levels [10].

According to literature data, bile ducts dilatation or Caroli syndrome occurs in 16.2–69.4% of ARPKD patients (Table 2).

In our study dilatation of bile ducts was found in 10/16 patients (62.5%). Mean age of diagnosis was higher than in other series: 7 vs. 3 years [19], but the diagnosis was based mainly on ultrasonography (US; less sensitive than other methods, ex. MRCP). Dilatation of common bile duct (CBD) was described in 5 patients in abdominal ultrasonography. In patients P8 and P16, who had MRCP, dilated CBD was detected previously by US.

In a large cohort reported by Gunay-Aygun *et al.* dilatation of CBD was found in 56% (n = 40) of ARPKD patients, most of them (n = 21) had no visible abnormalities of the intrahepatic biliary system. CBD dilatation coexist-

TABLE 2. Incidence of biliary tract dilatation and cholangitis in ARPKD

Publication	Dilated bile ducts or Caroli syndrome	Cholangitis
Burgmaier *et al*. [14]	3/14 (21.4%)	4/32 (12.5%)
Capisonda *et al*. [15]	12/27 (44.4%)	n/d
Dias *et al*. [16]	4/25 (16.0%)	1/25 (4.0%)
Guay-Woodford *et al*. [17]	24/148 (16.2%)	8/179 (4.5%)
Gunay-Aygun *et al*. [10]	50/72 (69.4%)	4/73 (5.5%)
Khan *et al*. [18]	5/14 (35.7%)	2/9 (22.2%)
Luoto *et al*.[19]	12/27 (44.4%)	2/27 (7.4%)
Shorbagi *et al*.[#] [4]	8/26 (30.8%)	6/26 (23.1%)

[#]Study group consists of patients with congenital hepatic fibrosis, not only in a course of ARPKD

ed with dilatation of peripheral intrahepatic bile ducts in 11 patients and with dilatation of peripheral and central medium-sized intrahepatic bile ducts in 8 [10].

Sometimes it is difficult to distinguish between cystic biliary dilatation and isolated liver cyst. This in an important distinction as isolated hepatic cysts is associated with lower risk of infection and cholangitis in comparison to ectatic biliary ducts [7].

In our cohort liver cysts were found in 6 patients. All but one (P17) had dilated bile ducts.

Incidence of cholangitis in ARPKD ranges from 4 to 23.1% (Table 2).

Only one our patient (P14) had documented cholangitis at the age of 31 years.

In other study mean age of diagnosis of cholangitis was 21.8 years (20.8–24.0) [14].

Cholangitis may occur earlier in life, especially in patients on immunosuppression after kidney transplantation [18, 19].

Correlation between cholangitis and dilated intrahepatic bile ducts was reported in some papers [17], however not in all [10].

There are no recommendations on proper timing for MRCP or high resolution ultrasonography (HR-US) examination in patients with negative history of cholangitis. In asymptomatic paediatric patients dilatation of intrahepatic bile ducts will not affect significantly further management. In patients prepared for kidney transplantation results on MRCP or HR-US may be crucial (increased risk of recurrent cholangitis due to immunosuppression; indication for combined kidney and liver transplantation). Moreover, in adolescents and young adults risk of cholangiocarcinoma should be considered [7, 13, 20, 21].

Our study faces some limitations.

The study group was small, however follow-up was relatively long (mean follow-up time after the initial diagnosis was 14 years, ranging from 6 to 37 years). What is essential and is the value of this work is the fact that all patients had molecularly confirmed diagnosis of ARPKD.

Retrospective nature of work caused that some data were not available for analysis. For example, data on biliary acids concentration were limited to three patients.

Different imaging methods were used to assess liver structure. All patients were done abdominal ultrasonography, however only few patients had liver scintigraphy, MRCP or CT. Therefore the number of patients with dilated bile ducts may be underestimated. In cohort presented by Gunay-Aygun *et al*. 40% had a specific type of Caroli syndrome in the form of lacy fusiform dilatation of peripheral intrahepatic bile ducts visible only on MRCP or HR-US [10].

CONCLUSIONS

In patients with ARPKD abnormalities of the biliary tract can occur even when standard laboratory tests findings stay within normal limits (these tests may be insufficient to detect liver involvement). Detailed biliary tree imaging evaluation should be performed in each patients with increased GGT activity/bile acid concentration, history of cholangitis, before kidney transplantation, as well as in adolescents and young adults due to increased risk of cholangiocarcinoma.

DISCLOSURE

The authors declare no conflict of interest.

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