Original Paper

The Role of Early Diagnosis of Hepatorenal Cystic (HRC) Syndrome in Children-Clinical Trial

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ABSTRACT: The hepatorenal cystic (HRC) syndrome is a heterogeneous group of severe monogenic conditions that may be detected before birth. Effective programme evaluation of children with HRC syndrome is a systematic way to identify the renal and urinary tract malformations which represent the most common cause of end-stage renal disease (ESRD). We conducted a study involving 50 patients, who were between 3 months and 16 years of age, with multiple admissions in the Nephrology Department of „Maria Sklodowska Curie" Children's Emergency Hospital from Bucharest, during 6 years (April 14th 2010-October 24th 2016), to evaluate the HRC syndrome. The admission symptomatology was mainly represented by the nephrology evaluation which was essential in the management of children's polycystic kidney disease. For example, a premature infant (gestational age=32 weeks) with positive heredo-collateral history (mother and grandmother were diagnosed with polycystic kidney disease), was tested positive for cystic renal disease after the fetal morphology was performed. It was also done a genetic determination for the presence of PKD1 and PKD2 mutations which are specific to autosomal dominant polycystic kidney disease-ADPKD. However, the genetic test was negative and a postnatal nephrological evaluation was performed using renal ultrasound. The image revealed autosomal recessive polycystic kidney disease-ARPKD. This study emphasizes the importance of an early diagnosis (prenatal, neontal, postnatal) correlated with the admission symptoms and also with the genetic diagnosis (mutations of PKD1 and PKD2).

KEYWORDS: *HRC syndrome, ARPKD, ADPKD, liver fibrosis, multicystic left/right dysplastic Kidney*

Introduction

The hepatorenal cystic (HRC) syndrome is a heterogeneous group of severe monogenic conditions that may be detected before birth. Commonly, HRC syndrome present in the neonatal and paediatric age, with consistent developmental abnormalities mostly involving the liver and kidney. The changes include the proliferation and dilatation of epithelial ducts in these tissues with abnormal deposition of extracellular matrix. In the liver, increased hepatic fibrosis often associates with cysts lined with biliary epithelium and a variable degree of intrahepatic biliary tract dilatation. Cystic lesions also affect the kidneys and their severity determines the clinical presentation and long term prognosis for the hepatorenal cystic syndrome [1,3].

According to the Romanian Society of Radiology and Medical Imaging, hepatorenal cystic syndrome is characterized by structural congenital disorders (Multicystic Dysplastic Kidney, Renal cystic dysplasia, Sponge kidney) and structural genetic disorders (Autosomal recessive polycystic kidney disease-ARPKD, Autosomal dominant polycystic kidney disease-ADPKD, Medullary cystic kidney disease, Nephronophthisis and Glomerulocystic kidney disease) [2].

Prenatal ultrasound is one of the most important radiological techniques used to evaluate the kidneys and urinary tract of a fetus. Congenital renal anomalies are the most common sonographically identified malformations. Fetal ultrasonography is able to reveal an early diagnosis of renal malformations in order to apply the adequate treatment and lower the perinatal and postnatal mortality rate. Both in the USA and Europe, there are tests and procedures to diagnose the urinary tract infections and renal anomalies for children up to 2 years old, which is the period of time when medical and surgical treatment are most likely to succeed. Effective programme evaluation of children with HRC syndrome is a systematic way to identify the renal and urinary tract malformations which represent the most

common cause of end-stage renal disease (ESRD) [9,10,11].

The aim of this study is to highlight the importance of early diagnosis of hepatorenal cystic (HRC) syndrome in children, using adequate therapeutic strategies, in order to delay the end-stage renal disease and minimize the adverse outcomes.

Patients and methods

We conducted a study involving 50 patients, who were between 3 months and 16 years of age, with multiple admissions in the Nephrology Department of „Maria Sklodowska Curie" Children's Emergency Hospital from Bucharest, during 6 years (April 14th 2010-October 24th 2016), to evaluate the hepatorenal cystic (HRC) syndrome. Prenatal diagnosis of polycystic kidney disease was considered positive after performing fetal ultrasonogrophy. The women assigned to the ultrasound test underwent ultrasonographic examination at 16-22 weeks of gestation. The positive ultrasonography results were correlated with genetic testing (PKD1 and PKD2 mutations are known to be associated with autosomal dominant polycystic kidney disease-ADPKD) and also with positive family history of polycystic kidneys. In case of inconclusive ultrasound results, a postnatal MRI was performed to confirm the diagnosis of polycystic kidney disease. Urinary tract infections (UTIs) diagnosis for symptomatic patients was based on positive urine culture (>/=10^5col/ml, single germ) and for asymptomatic patients, at least two positive samples in two different days (>/=10^5col/ml, same germ). Urine collection in sterile containers was made according to the age of patient, such as for the newborns and infants in plastic bags attached to the perineum, for cooperative and continent children, mid-stream urine sample, after a genito-urinary pre-wash or, as the case may be, suprapubic aspiration and catheterization. The diagnosis of UTIs was confirmed if the urine obtained by suprapubic aspiration revealed the growth of any number of bacteria except less than 2-3x10^3col/ml of coagulase-negative staphylococci, or after performing female urethral catheterization /obtaining a mid-stream urine sample from circumcised boys, in case of newborns and infants with fever and more than 50x10^3col/ml with single bacteria and also for 10-50x10^3col/ml accompanied by polakiuria. The imagistic investigations were performed at the „Maria Sklodowska Curie" Children's Emergency Hospital from Bucharest. All patients provided informed consent in written form, following the protocol approved by the local Ethics Committee. All study procedures were conducted in accordance with the Declaration of Helsinki; patients were not subjected to any maneuver outside normal diagnostic protocols.

Statistical analysis was performed using Microsoft Office Excel 2010.

For numerical variables, statistical mean differences were assessed using Student's t-test and ANOVA, while for categorical variables the chi-square test was used. Statistical difference was considered at p-levels under 0.05 (95% confidence). The graphs showing the results were created using Microsoft Office Excel 2010.

Results

Postnatal confirmation of prenatally diagnosed polycystic kidneys at 16-20 weeks gestational age was obtained for 20 patients after they undergone renal ultrasound. Neonatal diagnosis of polycystic kidneys was confirmed in 4 cases, and the postanatal diagnosis was positive in 26 cases for patients admitted to the hospital with non-specific renal symptomatology (Fig.1, Fig.3).

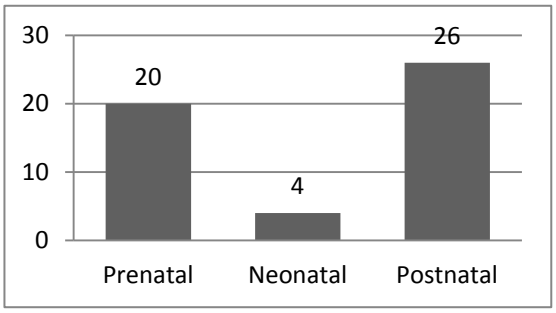

Fig.1. Distribution of patients according to the time of diagnosis

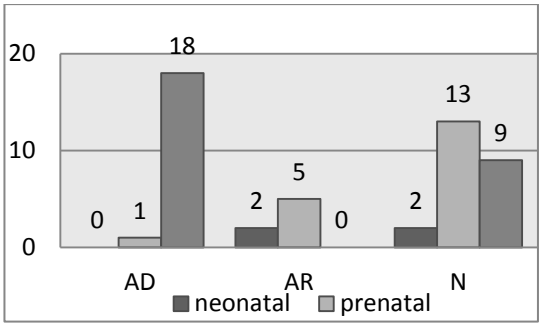

Fig.2. Distribution of patients according to the moment of diagnosis and the inheritance pattern of the renal cystic disease

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Table 1. Classification of patients according to the moment of diagnosis and the pattern transmission of the renal cystic disease

	Neonatal Diagnostic	Prenatal Diagnostic	Postnatal Diagnostic
AD	0	1	18
AR	2	5	0
N	2	13	9

AD=Autosomal dominant polycystic kidney disease-ADPKD

AR=Autosomal recessive polycystic kidney disease-ARPKD

N=Multicystic Left/Right Dysplastic Kidney, Renal cystic dysplasia with undetermined genetic transmission pattern.

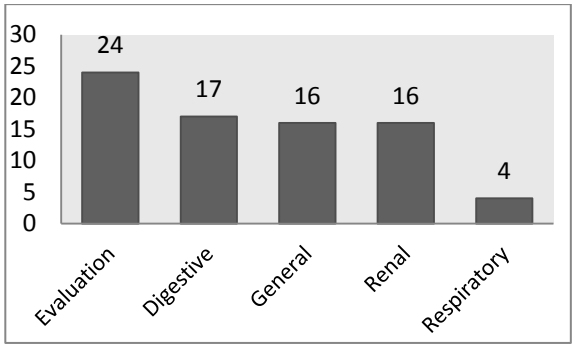

Fig.3. Admission symptomatology

The admission symptomatology was mainly represented by the nephrology evaluation which was essential in the management of children's polycystic kidney disease. For example, a premature infant (gestational age=32 weeks) with positive heredo-collateral history (mother and grandmother were diagnosed with polycystic kidney disease), was tested positive for cystic renal disease after the fetal morphology was performed. It was also done a genetic determination for the presence of PKD1 and PKD2 mutations which are specific to autosomal dominant polycystic kidney disease-ADPKD. However, the genetic test was negative and a postnatal nephrological evaluation was performed using renal ultrasound. The image revealed autosomal recessive polycystic kidney disease-ARPKD (Fig.4, 5). *PKD1gene* encodes an integral membrane glycoprotein, polycystin-1, that is implicated in cell-cell or cell-matrix interactions. The *PKD2* gene product, polycystin-2, has significant homology to a voltage-activated Ca2+channel in the intracellular C-terminal domain. Polycystin-1 and-2 appear to interact to form a heterodimeric ion channel at the plasma membrane that regulates renal tubular morphology and function [1].

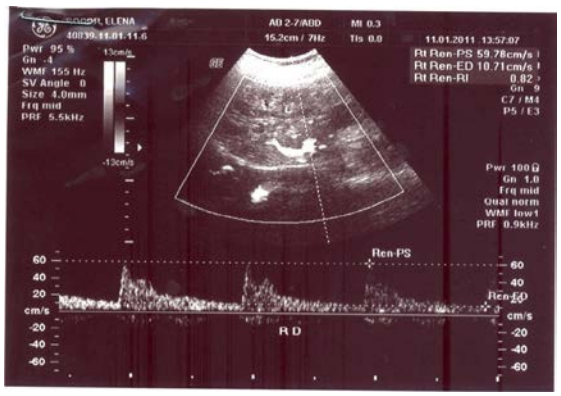

Fig.4. Renal ultrasound of the right kidney

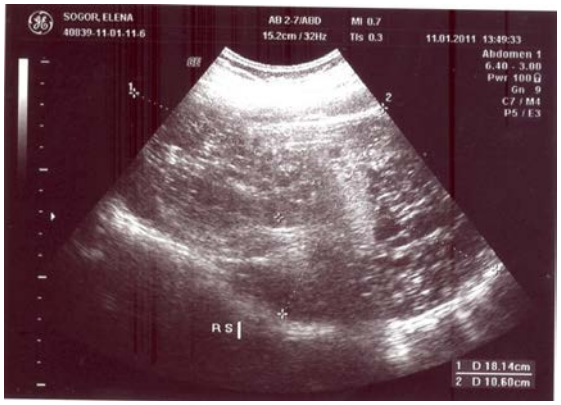

Fig.5. Renal ultrasound of the left kidney

Postnatal renal ultrasound revealed: enlarged normally located kidneys (Right kidney-18.2/10.6cm; Left kidney-17/8cm), the loss of bilateral corticomedullary diferentiation, renal parenchyma replaced by multiple cysts with a maximum diameter of 2,2cm in the inferior right pole and 2cm in the inferior left pole and right mild mediorenal caliectasis of 9mm. There was no evidence of nephrolitiasis or dilation of pyelocaliceal system, urinary bladder in semirepletion, transonic content, normal vesical wall. No fluid collection in the peritoneal recesses. Limited visualization of the ureters (Fig.4, 5).

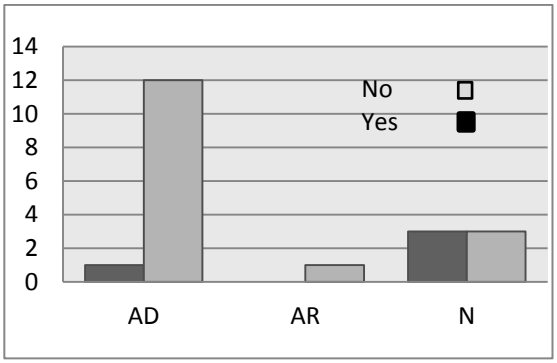

Fig.6. Genetic maternal inheritance of polycystic kidney disease

AD=Autosomal dominant polycystic kidney disease-ADPKD

AR=Autosomal recessive polycystic kidney disease-ARPKD

N=Multicystic Left/Right Dysplastic Kidney, Renal cystic dysplasia with undetermined genetic transmission pattern

Dominant maternal pattern of inheritance is emphasyzed in the autosomal dominant polycystic kidney disease-ADPKD.

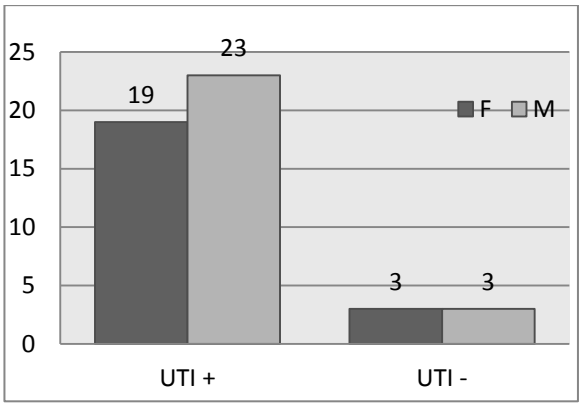

Fig.7. Classification of urinary tract infections by gender

There were 50 patients confirmed with polycystic kidney disease, 42 of them were diagnosed with UTIs, 6 were negative for UTIs and in 2 of the cases there was no evidence of it (Fig.6).

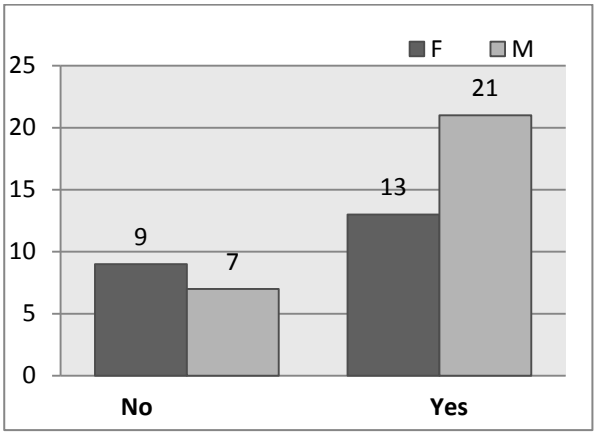

Fig.8. Presence of at least one urinary tract infection episode

Urinary tract infections incidence in men was represented by 21 cases out of a total number of 28 male patients and female patients were 13 out of a total of 22 cases.

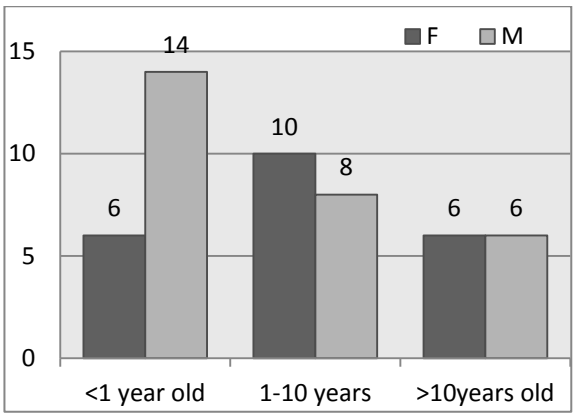

Fig.9. Age and gender distribution of the study group

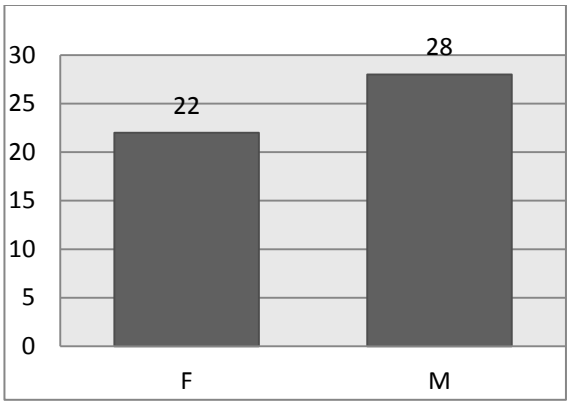

Fig.10. Distribution of female and male patients

Renal polycystic disease was confirmed for 22 female patients and 28 male patients. The female/male ratio aged 0-1 year old was R=6/14, for 1-10 years old R=10/8 and over 10 years old, R=6/6 (Fig.9, 10).

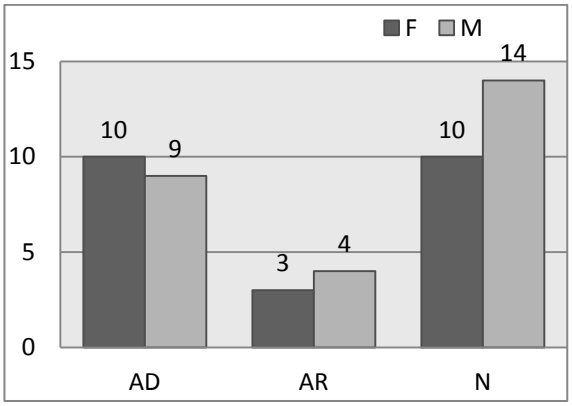

Fig.11. Patients distribution in accordance with the inheritance pattern

AD=Autosomal dominant polycystic kidney disease-ADPKD

AR=Autosomal recessive polycystic kidney disease-ARPKD

N=Multicystic Left/Right Dysplastic Kidney, Renal cystic dysplasia with undetermined genetic transmission pattern

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Autosomal dominant polycystic kidney disease-ADPKD was diagnosed in 10 female patients and 9 male patients, ARPKD (AR pattern) was confirmed at 3 female patients and 4 male patients, both Multicystic Left/Right Dysplastic Kidney and Renal cystic dysplasia with undetermined genetic transmission pattern were positive for 10 female patients and 14 male patients.

Discussion

Our study revealed that 18 out of 19 patients with autosomal dominant polycystic kidney disease (AD) were postnatally diagnosed, unlike those patients with ARPKD who were mainly prenatally diagnosed.

These results are in concordance with medical literature which states that only 2% of the patients with ADPKD, experience symptoms before the age of 15 years old. Prenatal diagnosis of ARPKD can be suspected starting with the 15th week of gestational age based on hyperechogenic enlarged kidneys. Oligohydramnios can be diagnosed around the 20th week of gestation accompanied by enlarged kidneys, absent bladder or its reduced dimensions [4,12]. In contrast to the patients with ARPKD, most patients with ADPKD are born with apparent normal kidneys and they are admitted to the hospital with high blood pressure and kidney failure, usually when the renal parenchyma is mainly replaced by cysts. Patients with ADPKD present an insidious evolution and are mainly diagnosed when they are admitted to the hospital with complications and symptoms specific to the cysts' mass effect, as well as infection and intracystic hemorrhage. They also have an increased risk of developing cardiovascular complications, aneurysms and aortic dissections. Usually, children with ADPKD are diagnosed after performing a screening using abdominal ultrasound or during the investigation of other pathologies [7,13].

The anamnestic data present in the patients' records sustain the maternal inheritance pattern of ADPKD. Multiple studies have reported a different evolution of patients with autosomal dominant polycystic kidney disease depending on gender, known as „genomic imprinting". Therefore, if a male patient is diagnosed with ADPKD and this disease is inherited from his mother, then the prognosis is more severe with an earlier evolution towards end-stage renal disease, than if he had inherited the disease from his father and the evolution to ESRD is delayed [8,14].

The main symptoms of admission in the hospital were represented by the nephrological evaluation, which was essential in the management of children's polycystic kidney disease and as well as establishing an accurate diagnosis. Nephrological re-evaluation of the premature infant (gestational age=32weeks) with positive heredo-colaterall history (mother and grandmother were diagnosed with polycystic kidney disease) tested negative for ADPKD (absence of PKD1 and PKD2 mutations), confirmed postnatal the ARPKD diagnosis.

A relevant aspect is sustained by the increased incidence of UTIs (positive diagnosis of UTIs at 42 out of 50 patients with polycystic kidney disease) [5,6].

Moreover, our study revealed a higher incidence of urinary tract infections in male patients than in female patients. These data contradict the medical literature which states that UTIs are more frequent in female patients than in male patients. After the first year of life, UTI's incidence in boys drops to 0.08%, while girls' incidence is maintaining at 3-4% until the age of 6 years old. The higher incidence of female patients was attributed to relatively short urethra [11]. We have also identified the main affected age group as for the boys under 1 year old, following age group equalization. Sex distribution related to the inheritance pattern respects the statistical data from literature which states that ADPKD is more common in female patients, and ARPKD among male patients [3,6]. According to recent studies, the infantile form of ARPKD's evolution is to early exitus, after birth, due to kidney and/or heart failure. Young children with ARPKD survive up to 15 years old; the symptomatology is dominated by the liver disease which develops cirrhosis. Prenatal diagnosis of ARPKD is extremely important due to the risk of dystocia caused by giant renal masses. ADPKD is accompanied by liver cysts, while ARPKD is accompanied by hepatic fibrosis and secondary portal hypertension. Many studies have reported gender differences in ADPKD's evolution: progression to end-stage renal disease is faster (with about 6 years) in men than in women, and hepatic cysts occur earlier, are numerous and larger in female cases. In ADPKD, the ESRD occurs later, in adult life, while in ARPKD the ESRD installs earlier, during childhood. Liver complications are in fact represented by the complications of the cysts as infections, intracystic hemorrhages, cystic rupture and also by the mass effect complications which are a cause of numerous

and enlarged cysts: simple discomfort, abdominal distension, cholestasis and portal hypertension [15].

Conclusion

This study emphasizes the importance of an early diagnosis (prenatal, neonatal, postnatal) correlated with the admission symptoms (urinary tract infections being present in almost all cases of ADPKD, ARPKD and Multicystic Left/Right Dysplastic Kidney, Renal cystic dysplasia with undetermined genetic transmission pattern) and also with the genetic diagnosis (mutations of PKD1 and PKD2)-in cases when it was possible to achieve it. It has been identified the maternal inheritance pattern of ADPKD, and therefore the anamnesis has a strong role, positive history of ADPKD in the family could help in establishing the diagnosis. The results are in concordance with the literature data, female patients are most likely to develop ADPKD, in contrast to male patients who develop ARPKD.

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All authors had equal contribution.

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