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BRIEF REPORT

Renal outcome in children with antenatal diagnosis of severe CAKUT

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Abstract
Background Congenital abnormalities of the kidney and the urinary tract (CAKUT) are among the most frequent causes of antenatal consultation. In this retrospective study we evaluated the outcome of children for whom antenatal consultation was performed between 2006 and 2011 in one single pediatric nephrology center, with a particular focus on the outcome of children whose parents declined a therapeutic abortion.
Case–Diagnosis/Treatment Thirty-four cases of isolated CAKUT were found. Of these, 19 terminations of pregnancies (TOP) were proposed, and ten TOP were refused for these patients. Among the ten infants whose parents refused an abortion, five died in the first month of life. Their median creatinine level at 3 days of life was 56 (range 25–316) μmol/L. For the five surviving patients, the median age at the time of analysis was 29 months, at which time all had a normal serum creatinine with a variable degree of proteinuria.Oligohydramnios was found in three of the patients who died. However, two of the five surviving patients also had oligohydramnios.
Conclusion In ten patients for whom TOP was proposed for severe CAKUT and refused, five had normal serum creatinine at a median age of 29 months. No one predictive factor seems to have sufficient specificity to motivate a therapeutic abortion proposal, suggesting the need of long-term follow-up studies.

Keywords CAKUT · Oligohydramnios · Antenatal diagnosis · Outcome · Termination of pregnancy

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Introduction

Congenital abnormalities of the kidney and the urinary tract (CAKUT) are among the most frequent causes of antenatal consultation and occur in 1/500 live births [1]. The number of discovered gene defects related to CAKUT is constantly increasing, resulting in a complicated gene network [1, 2]. Epidemiologic data on renal outcome in children with congenital CAKUT are lacking even though pediatric nephrologists are being increasingly consulted. In this preliminary retrospective study we evaluated the outcome of children for whom an antenatal consultation was performed between January 2006 and February 2011 in one single pediatric nephrology center, with a particular focus on the outcome of children whose parents declined termination of pregnancy (TOP).

Patients and methods

To be eligible for the study, patients had to have been referred to the Pediatric Nephrology unit at Trousseau

Hospital by the consulting obstetrician for an antenatal diagnosis of CAKUT without any other visible ultrasound abnormalities.

Data were collected from the mother's pregnancy obstetrical file (including the systematic antenatal ultrasound screening at 12, 22, and 32 weeks gestational age), the patient file, and the radiology and biochemical units' databases. We classified the patients into five groups according to their abnormalities: unilateral renal hypodysplasia, bilateral renal hypodysplasia, posterior urethral valves, multicystic dysplastic kidney, and isolated urologic abnormalities. The ultrasound evaluation was performed by an experienced radiologist on an Aplio XG ultrasound system (Toshiba, Tokyo, Japan) and the renal abnormalities evaluated as follows: (1) hypoplasia was defined as a kidney length smaller <2 SDS (standard deviation score) according to charts of fetal kidney size [3]; (2) dysplasia was suspected when the kidney was found to be hyperechogenic; (3) an oligohydramnios was suspected when the amniotic index (AI) was <8. When these data were not available, we used deep pocket measurements according to Queenan et al. [4]. TOP was proposed for bilateral renal abnormalities associated with oligohydramnios, which is considered to be a marker of early severe renal function impairment, or for bilateral renal abnormalities without oligohydramnios but with severe parenchyma abnormalities compatible with the development of end-stage renal disease (ESRD) during childhood.

Pathology examinations were performed in the fetal pathology unit of Trousseau hospital. The presence of functional renal parenchyma, pulmonary hypoplasia defined by a lung weight/body weight ratio <0.012, and the association of other morphological or histological abnormalities were assessed.

Results

Thirty-four cases of isolated CAKUT were found, for which 19 TOP were proposed; the parents refused TOP for ten of these patients (Table 1). TOP was proposed for the 12 patients for whom oligohydramnios was found and for the seven cases of bilateral renal hypodysplasia without oligohydramnios. No abortion was proposed for unilateral abnormalities nor for abnormalities of the urinary tracts without renal injury (Tables 1, 2). Among the ten patients for whom a TOP was refused, five died in the first month of life. The median creatinine level at 3 days of life was 162 (range 25–358) μmol/L. The median time of hospitalization was 10 (range 2–80) days. The abnormalities seen on the prenatal ultrasounds were confirmed by postnatal exams. Oligohydramnios was found in the five patients who died. However, two of the five surviving patients also had an oligohydramnios. Among the three patients without oligohydramnios for whom ultrasound abnormalities had been considered severe enough to propose TOP, all had normal renal function at the age of 60, 55, and 15 months, respectively. One patient had an increased fetal beta-2 microglobulin blood level (9 mg/L); at the age of 29 months this patient had a normal serum creatinine level and significant proteinuria.

For the five surviving patients, the median age at the time of analysis was 29 months. All five surviving patients had a normal serum creatinine level, three without proteinuria and two with intermittent proteinuria, with a maximum urinary creatinine level of 182 and 235 mg/mmol, respectively. Among these five patients none had hypertension or required anti-hypertension medication (Table 3).

Among the nine TOP, a pathologic examination was performed on six fetuses (Table 4): three had an echographic diagnosis of oligohydramnios and four had a pulmonary hypoplasia. All had abnormal nephron structure or at least a reduction in nephron number. Five had associated morphological abnormalities, such as hypertelorism, ventricular septum hypertrophia, incomplete small pulmonary scissure (2 patients), pseudocysts in the cortex of the adrenal glands (2 patients), accessory spleen, xiphoida bifida, and pulmonary anatomy abnormalities (2 patients). One patient had autosomal recessive polycystic kidney disease (ARPKD) with liver and pancreas fibrosis.

An ultrasound control was performed after birth for seven of the 15 patients. The antenatal diagnosis was confirmed in six of these seven patients; in the seventh patient, the

Table 1 Patient characteristics by category

Category (n)	Mean age at diagnosis (GW)	Oligohydramnios	Termination of pregnancy proposal	Termination of pregnancy
URHD (2)[a]	35	0	0	0
BRHD (14)	26.8±3.6	4	10	4
PUV (4)	29	4	4	1
MCKD/PKD (12)	24.3±4.7	4	5	4
IUA (2)	28	0	0	0

GW, Gestational weeks; URHD, unilateral renal hypodysplasia; BRHD, bilateral renal hypodysplasia; PUV, posterior urethral valves; MCDK, multicystic dysplastic kidney; PKD, polycystic kidney disease; IUA, isolated urologic abnormalities

[a] Patient number in each group is given in parentheses

Table 2 Ultrasound parameters of patients for whom a termination of pregnancy was proposed

Patient number	Right kidney size SDS	Left kidney size SDS	Age at oligamnios	Lowest amniotic fluid index (AFI)	Echogenicity	Cysts (localization, number)	Urologic abnormalities[a]	Termination of pregnancy[a]
1	> +3	>+3		12	Bilateral hyperechogenicity, LD	0	0	0
2	+3	+3		No oligohydramnios	Bilateral hyperechogenicity, LD	Bilateral, multiple	0	0
3	< −3	>+3		8.5	R: LD; L: Hyperechogenicity	Unilateral, multiple	1	0
4	−3	+1.5	34	0	Bilateral hyperechogenicity	0	1	0
5	>+3	+2		8	Bilateral LD, L: Hyperechogenicity	Bilateral, multiple	1	0
6	>+3	>+3		No oligohydramnios		Bilateral, multiple	0	0
7	>+3	+3	31+2	6	Bilateral hyperechogenicity, LD	Bilateral, multiple	0	0
8	+2	−2	32+6	9	R: Multicystic dysplasia, L: LD	Unilateral, multiple	1	1
9	< −2	>+3		12	Bilateral hyperechogenicity, LD	0	1	1
10	None	+2	28+2	6.5	Hyperechogenicity, LD	0	1	1
11	>+3	>+3		No oligohydramnios	Normal, MRI: Renal sinus lipomatosis	Bilateral, multiple	0	1
12	>+3	>+3	22	0.2	Bilateral hyperechogenicity, LD	Bilateral, multiple	0	1
13	>+3	>+3	28+4	0	Bilateral hyperechogenicity, normal differentiation	Bilateral, multiple	1	0
14	>+3	>+3	22	0	Bilateral hyperechogenicity, LD	Bilateral, multiple	1	0
15	>+3	>+3	32	0	Bilateral hyperechogenicity, LD	Unilateral, one	1	1
16	>+3	>+3	33+3	0	Inversion of differentiation, hyperechogenic medulla	Bilateral, multiple	0	1
17			22+5	0	Bilateral hyperechogenicity, LD	Bilateral, multiple	0	1

'SDS, Standard deviation score; R, right; L, left; LD, loss of differentiation; MRI, Magnetic resonance imaging

[a] 0, Absence; 1, presence

Table 3 Follow-up data of surviving patients for whom termination of pregnancy was declined by the parents

Patient no./ gender	Birth term (weeks, GA)	Age at last follow-up (months)	Prenatal US[a]	Neonatal US[a]	US at last follow-up[a]	Serum-creatinine	Maximal proteinuria during follow-up	Proteinuria (mg/mmol creatinine)	BP
1/M	38+1	4	RH1 H1 LD1 C0 U0	RH1 H0 LD0 C0 U0	RH1 H0 LD0 C0 U0	15	< 20	< 20	< +2DS
2/M	39	63	H1 LD1 C1 U0	RH0 H1 LD1 C1 U0	RH0 H1 LD1 C1 U0	28	187	< 20	< +2DS
3/M	40	29	Rh right RH left H1 LD1 C0 U1	Rh right RH left H0 LD0 C0 U1	RH left H0 LD0 C0 U1	42	< 20	< 20	< +2DS
4/M	35+5	36	Right:Rh1 H1 LD1 C0 U1, Left:RH0 U0	Right:Rh1 H1 LD1 C0 U0, Left:RH0 U0	Right:Rh1 H1 LD1 C0 U0, Left:RH0 H1 LD1 U0	66	235	< 20	< +2DS
7/M	38	1	RH1 H1 LD0 C1 U0	RH1 H1 LD0 C1 U0	RH1 H1 LD0 C1 U0	18	< 20	< 20	< +2DS

GA, Gestational age; US, Ultrasound; BP, blood pressure; M, male; F, female; Rh, renal hypoplasia (kidney size<−2 SDS; RH, renal hypertrophy (kidney size >2SDS); H, Hyperechogenicity; C, cyst; U, urinary tract abnormalities

[a] 0, Absence; 1, presence

abnormality was found to be bilateral, whereas the prenatal exam had found it to be unilateral. Serum creatinine and proteinuria were checked in only two patients and found to be normal at 5 months and 3 years of age, respectively.

Discussion

Oligohydramnios has been found to be independently associated with a poor renal outcome [5]. In our study, among the seven patients born alive with oligohydramnios, five died in the first month of life. However, if there are no abnormalities other than the renal ones and no early oligohydramnios, which exposes the patient to pulmonary hypoplasia, nephrologic management is still possible and has to be discussed with the parents.

Even though the requirement of neonatal peritoneal dialysis and renal transplantation after the first year of life is regularly discussed with the parents in such clinical settings, it had not been performed in our patients. Kemper et al. found similar results in ten patients with oligohydramnios, in which only one patient required peritoneal dialysis and another preemptive renal transplantation after a 2.5-year follow-up [6].

Patients without oligohydramnios had normal renal function after long-term (1–5 years) follow-up, the ultrasound scan revealing severe abnormalities and the TOP proposal. This strengthens the concept that oligohydramnios is a risk factor for early renal failure and that in its absence it is very difficult to evaluate the duration of time to progress to end-stage renal failure. Nevertheless, the considerable phenotypic changes over time for many patients makes pre-natal counseling extremely difficult since although abnormalities often worsen over time, on rare occasions improvement has also been observed.

An increased blood or amniotic fluid beta-2-microglobulin level has been reported to be associated with a poor renal outcome [7]. However, in a meta-analysis which evaluated the intrinsic validity of beta-2-microglobulin dosage, Morris et al. demonstrated that it was of little diagnostic help, especially in amniotic fluid with poor specificity [positive predictive value +2.92, confidence interval (CI) 1.28–6.67; negative predictive value −0.53, 95% CI 0.24–1.17] [8]. Moreover, the beta-2-microglobulin level has been found to be increased in several fetal infections, such as cytomegalovirus and toxoplasmosis [9]. Therefore, the beta-2-microglobulin level seems to be of limited value in the context of a TOP. In our study, the fetal beta-2-microglobulin blood level was tested in only one case, in which it had increased to 9 mg/L, associated with an oligohydramnios. The parents refused a TOP, and the patient had severe neonatal renal failure but did not require dialysis. The renal function recovered, and this patient had a normal

Table 4 Fetal pathology data

Patient number	Age at TOP (weeks)	Right kidney size (SDS)	Left kidney size (SDS)	Renal parenchyma	Urinary tract	Histology	LW/BW	Other abnormalities
8	36+5	> +3	<−3	Right kidney: multicystic; Left: Cortical cysts, no LD	Right: ureteral duplication without communication with bladder	R: Few glomeruli, cartilage islets, L:3–4 bands of glomeruli, conjunctive tissue++, eosinophilic tubular infiltration	0.01	Hypertelorism, ventricular septum hypertrophia, incomplete small pulmonary scissure
9	34+3	+3	0	Right kidney: hemorragic	Right: pyelic dilatation; Left: ureteropelvic-junction syndrome	R: Normal nephron structure, tubular dilatation, some glomeruli with peripheral fibrosis	0.017	Xyphoida bifida, right lung with 4 parts
10	30	None	+2	Horseshoe, cortical size 2 mm, medulla size 3 mm	Important pyelic dilatation	Reduced renal blastema, Few mature glomeruli	0.01	0
11	33+3	>+3	>+3			R: Reduced renal blastema, few nephron structures; L: More nephron structures, minor diminution of the number of glomeruli	0.027	hexadactily *4, 2 accessory spleen, incomplete small pulmonary fissure
12	29+3	>+3	>+3	Bilateral cysts	0	Normal renal blastema, few mature glomeruli, cysts EMA+, CD10-	0.01	liver portal fibrosis, pancreatic fibrosis, pseudocystic cortex of the adrenal glands
17	22+5			Bilateral cysts	Bladder atrophia, ureteral dilatation	Reduced renal blastema, no normal nephron	0.01	Cranio-facial dysmorphia (anamnios), pseudocystic cortex of the adrenal glands

Fetopathology data were available for six fetuses

TOP, Termination of pregnancy; LW/BW, lung weight/body weight ratio<0.012 pulmonary hypoplasia; EMA, expression of MUC1

serum creatinine level with a proteinuria of 235 mg/mmol urinary creatinine at the age of 2.5 years.

The follow-up of patients for whom no TOP had been proposed was difficult since approximately 50% of patients were lost to follow-up. This jeopardizes data interpretation. Nevertheless, the great importance of a long-term follow-up of those patients should be emphasized as morphological presentation of CAKUT (i.e., development of contralateral lesions) may change over time, and hyperfiltration lesions with secondary development of proteinuria may occur despite the initial absence of pathologic urinary and blood parameters. Sanna-Cherchi et al. [10] evaluated the renal outcome of patients with CAKUT at 30 years of age. In this study, the authors followed 312 patients with an antenatal or postnatal diagnosis of CAKUT and found ESRD in 58 patients (19%) by the age of 30 years if all types of CAKUT were taken into account. Even in groups considered at low risk of ESRD and for whom a TOP is usually not proposed, the patients had a worse outcome than generally expected: among 27 patients initially diagnosed with unilateral hypodysplasia, four patients required dialysis at the age of 30 years. Even though parents with fetuses carrying unilateral lesions have to be reassured, it seems to be of extreme importance to organize a long-term follow-up of those patients in order to be able to initiate a nephroprotective strategy in the case that microalbuminuria or hypertension develops. The limits of sonographic and biologic prognosis factors leads to a discussion of the possibility of preconception genetic counseling since the number of genes known to be implicated in CAKUT is steadily increasing. However, most mutations are of autosomic dominant inheritance with an extreme variability in phenotype, which makes the prediction of severe kidney dysfunction impossible.

In conclusion, in the ten patients with severe CAKUT, for whom TOP was refused by the parents, five had a normal serum creatinine level at a median age of 29 months. This result demonstrates the difficulty in evaluating renal outcome in such patients. No single predictive factor seems to have enough specificity to motivate a TOP proposal, even the presence of an oligohydramnios. This finding suggests the need of long-term follow-up studies and new predictive markers.

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References

1. Song R, Yosypiv IV (2011) Genetics of congenital anomalies of the kidney and urinary tract. Pediatr Nephrol 26:353–364
2. Chen F (2009) Genetic and developmental basis for urinary tract obstruction. Pediatr Nephrol 24:1621–1632
3. Chitty LS, Altman DG (2003) Charts of fetal size: kidney and renal pelvis measurements. Prenat Diagn 23:891–897
4. Queenan JT, Thompson W, Whitfield CR, Shah SL (1972) Amniotic fluid volumes in normal pregnancies. Am J Obstet Gynecol 114:34–38
5. Oliveira EA, Diniz JS, Cabral AC, Leite HV, Colosimo EA, Oliveira RB, Vilasboas AS (1999) Prognostic factors in fetal hydronephrosis: a multivariate analysis. Pediatr Nephrol 13:859–864
6. Kemper MJ, Neuhaus TJ, Timmermann K, Hueneke B, Laube G, Harps E, Mueller-Wiefel DE (2001) Antenatal oligohydramnios of renal origin: postnatal therapeutic and prognostic challenges. Clin Nephrol 56:S9–S12
7. Dommergues M, Muller F, Ngo S, Hohlfeld P, Oury JF, Bidat L, Mahieu-Caputo D, Sagot P, Body G, Favre R, Dumez Y (2000) Fetal serum beta2-microglobulin predicts postnatal renal function in bilateral uropathies. Kidney Int 58:312–316
8. Morris RK, Quinlan-Jones E, Kilby MD, Khan KS (2007) Systematic review of accuracy of fetal urine analysis to predict poor postnatal renal function in cases of congenital urinary tract obstruction. Prenat Diagn 27:900–911
9. Dreux S, Rousseau T, Gerber S, Col JY, Dommergues M, Muller F (2006) Fetal serum beta2-microglobulin as a marker for fetal infectious diseases. Prenat Diagn 26:471–474
10. Sanna-Cherchi S, Ravani P, Corbani V, Parodi S, Haupt R, Piaggio G, Innocenti ML, Somenzi D, Trivelli A, Caridi G, Izzi C, Scolari F, Mattioli G, Allegri L, Ghiggeri GM (2009) Renal outcome in patients with congenital anomalies of the kidney and urinary tract. Kidney Int 76:528–533