

Renal tubular dysgenesis-a case presentation

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SUMMARY: Atasay B, Günlemez A, Arsan S, Bakkaloğlu S, Tulunay Ö, Yalçinkaya F. Renal tubular dysgenesis-a case presentation. Turk J Pediatr 2004; 46: 362-365.

Renal tubular dysgenesis (RTD) is a lethal, developmental anomaly of the fetal kidney characterized by a defect in differentiation of the proximal and distal convoluted tubules. It is usually associated with oligohydramnios in later pregnancy and Potter's syndrome. A neonate with typical features who presented with mild respiratory distress, dysmorphic appearance and anuria is described. At the age of seven days, peritoneal dialysis was started and was continued until the death of the baby at the age of three months. The diagnosis was made on the bases of clinical and ultrasonographic findings confirmed by renal biopsy. A review of the literature showed that this is the first case of RTD reported in Turkey.

Key words: newborn, anuria, renal tubular dysgenesis.

Renal tubular dysgenesis (RTD), with poorly developed proximal convoluted tubules, has been reported as a primary autosomal recessive congenital disorder¹, variably resulting in the features of Potter's syndrome. A similar tubular lesion due to antenatal tubular atrophy as a result of twin-to-twin transfusion syndrome or due to fetal exposure to angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists has been mentioned^{1,2}. We report a newborn with typical clinical and pathologic features of this rare disease, who presented with anuria and dysmorphological features in the absence of severe pulmonary disease.

Case Report

A four-day-old female infant was transported to our hospital because of anuria and respiratory distress. The baby was born to a 30-year-old mother by spontaneous vaginal delivery at 39 weeks of gestation. Though early pregnancy was uncomplicated, during the second half of the gestation the mother noticed that her abdomen was not expanding. During the pregnancy she was neither examined by a physician nor exposed to any drug. The parents are first cousins and had already lost the male

product of the previous pregnancy in the neonatal period. This deceased sibling had no specific diagnosis.

The baby was born small for gestational age and was resuscitated and given oxygen for the first three days of life at the local hospital. On admission the patient's weight was 2390 g, length 46 cm, head circumference 30 cm, body temperature 36.2°C, pulse rate 138/min, blood pressure 64/22 mmHg and respiration rate 65/min. The patient had mild respiratory distress and poor muscle tone. No urine had been passed since birth. Physical examination showed microcephaly, extremely wide sagittal and coronal sutures (2 cm) and very large fontanelles (anterior fontanelle 4x6 cm, posterior fontanelle 3x2 cm), low-set ears, high-arched palate, short neck, flexion deformity of wrist, and rocker bottom feet. The kidneys were not palpable.

Laboratory analysis revealed increased blood urea nitrogen and serum creatinine level, hyperkalemia, hyperuricemia and metabolic acidosis. ACE level was 5 U/L (normal newborn level >35 U/L). Renal ultrasonography (USG) demonstrated kidneys of normal size and shape (right: 4x2 cm, left: 4x2x1.6 cm) without hydronephrosis or macroscopic cysts. The

corticomedullary differentiation was indistinct. Doppler USG of abdominal aorta and renal vessels was normal.

On the 7th day of life peritoneal dialysis was started. An open renal biopsy was performed, the next week. Renal biopsy fixed in 10% formalin was examined with hematoxylin-eosin staining. Renal histology consisted of focal minimal tubular dilatation, in abnormally developed tubules, and crowded glomeruli with focal dilatation of Bowman's space together with increased interstitial connective tissue, which gave the impression of decreased tubular formation. The proximal convoluted tubules within undifferentiated renal tubules with little development of lumen structures were difficult to identify. There were a few tubules with cuboidal epithelial cells having larger and partly granular cytoplasm resembling abnormal proximal tubules (Figs. 1 and 2). One small corticomedullary area with inconsistent interstitial inflammatory cells was observed. Immunohistochemical studies for epithelial membrane antigen (EMA, Novacastra, 1:300), lysosyme (LYS, Neomarkers, 1:100) and alpha 1-antitrypsin (A1AT, Immunon, 1:200) were performed. When using antibodies against LYS and A1AT, the sections were pretreated with 0.1% trypsin (Sigma) and protease (Sigma), respectively, for 3 min at 37°C. No pretreatment was performed when using antibody against EMA. Antigen retrieval was performed with a microwave for 5x5 minutes in a citrate buffer solution. Nearly all the tubules were positive for EMA, whereas A1AT staining did not reveal any positivity in the tubules. Occasional LYS-

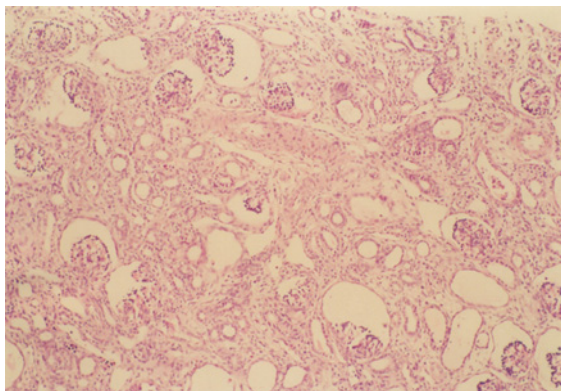


Fig. 1. Glomeruli appear crowded and all tubules are small and primitive with defective proximal tubular differentiation. Arterial-arteriolar wall thickness is visible, (H&E x 25).

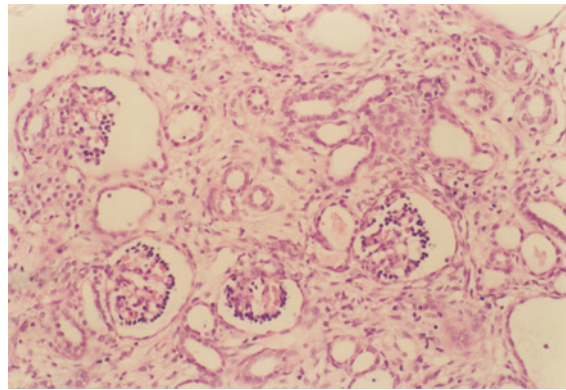


Fig. 2. Close-up view of the renal cortical pranchyma. Undifferentiated tubules do not demonstrate usual light microscopic characteristics of proximal or distal convolutions. Interstitial fibrosis separates tubules, (H&E x 50).

positive tubules and immunostained hypertrophied parietal layer cells of the glomerular capsule were found.

In the 2nd week of life edema and hypertension became prominent.

In the 8th week of peritoneal dialysis the patient underwent abdominal surgery and intestines were partially resected because of necrotizing enterocolitis developing as a result of peritonitis. The child died of overwhelming sepsis at the age of three months. Clinical and pathological manifestations of the case are summarized in Table I.

Table I. Clinical and Pathological Manifestations of the Present Case

| Clinical manifestations | |
|----------------------------------|--------|
| Sex | Female |
| Gestational age (weeks) | 39 |
| Age at death (days) | 124 |
| Oligohydramnios | + |
| Potter sequence | + |
| Microcephaly | + |
| Wide sutures/fontanelles | + |
| Congenital heart defect | - |
| Pathological findings | |
| Kidney size | Normal |
| Corticomedullary demarcation | Poor |
| Reduced/absent proximal tubules | + |
| Primitive tubule differentiation | + |
| Normal glomerulogenesis | + |
| Renal vascular abnormality | - |
| Parental consanguinity | + |

Discussion

The causes of anuria in the newborn period can either be pre-renal, i.e. developing secondary to perinatal asphyxia or dehydration; or renal, i.e. secondary to acute tubular and cortical necrosis, polycystic renal disease, bilateral renal agenesis, bilateral renal dysplasia, or renal vein thrombosis; or post-renal, such as in bilateral ureteropelvic stenosis, obstruction or posterior urethral valve. In this particular case, the presence of consanguinity and a sibling loss, Potter's phenotype, anuria with relatively late onset edema and hypertension, and other primary renal pathologies ruled out via Doppler and conventional USG, led us to the clinical diagnosis of RTD³. This initial diagnosis was later confirmed by a renal biopsy.

The pathological features of RTD are as follows^{1,3}: 1) the number of glomeruli and their morphology are normal; 2) proximal tubules are immature and their luminal structures are unclear, lacking brush borders; and 3) nearly all the tubules are EMA-positive on immunostaining, while proximal tubules in normal kidneys are EMA-negative. The present case fulfilled the above criteria. LYS was found to be a component of the brush border membrane of the proximal tubules⁴. Occasional A1AT and LYS-positive tubules was consistent with proximal tubules. More tubules with undifferentiated features showed EMA positivity, demonstrating that they were distal convoluted and collecting tubules⁵. The cystic dilatation of Bowman's space in some glomeruli might be consistent with one of the categories of glomerulocystic disease described by Bernstein et al.⁶, in that glomerular cysts were with dysplastic kidneys, as in this case. The decrease in amniotic fluid is presumably related to RTD. Oligohydramnios sequence and Potter's phenotype are associated with this renal anomaly in which renal function is absent. Both in the hereditary form (a developmental defect originating mid-gestation) of RTD, and in ACE inhibition fetopathy, as well as in the donor twin-to-twin transfusion syndrome, an ischemic insult causing the alteration of glomerular perfusion can result in impaired differentiation of the proximal tubules⁷⁻¹¹.

Studies published during the last decade have clearly established that the rennin-angiotensin system is necessary for normal development of

the tubules and the blood vessels of the kidney. Lack of angiotensin II in the rat causes a characteristic renal pathology including grossly distorted arterial vasculature and tubular atrophy¹². Renal lesions described in experimental animals resemble the renal histological abnormalities observed in human fetuses and newborns with ACE inhibitor fetopathy¹². Angiotensin II (via AT-1 and AT-2 receptors), epidermal growth factor and platelet derived growth factor play an important role in growth and differentiation of the fetal kidney¹³⁻¹⁵. In this patient, ACE inhibition due to a hereditary defect might have occurred in mid-gestation, resulting in impaired proximal tubular differentiation. Biopsy findings and also absence of hypertension in the first postnatal days despite anuria and presence of very low serum levels of ACE may support this hypothesis in the present case. The presence of a hypocalvaria suggests a disrupted perfusion of the membranous bones in addition to the renal insult¹⁶⁻¹⁸. In the cases described by Swinford et al¹⁹, 'wide fontanelles' were noted in one patient with decreased bony cortex of the skull, and in a case described by Russo et al.²⁰, 'widely patent cranial fontanelles' were present in an infant with RTD from a family with acrocephalosyndactyly syndrome. The absence of pulmonary hypoplasia as a part of the oligohydramnios sequence might be due to late development of oligohydramnios in the second trimester^{21,22}. As this pathology occurs in the second trimester, early pre-natal diagnosis is not possible. But in the presence of family history and consanguinity, the presence of oligohydramnios in the absence of genitourinary structural abnormalities may suggest the diagnosis. Upon diagnosis, the parents need to be informed about the poor prognosis and the 25% risk of recurrence in future offsprings.

REFERENCES

1. Allanson JE, Pantzar JT, MacLead PM. Possible new autosomal recessive syndrome with unusual renal histopathological changes. *Am J Med Genet* 1983; 16: 57-60.
2. Barr M, Cohen MM. Ace inhibitor fetopathy and hypocalvaria. *Teratology* 1991; 44: 485-495.
3. Tsukiyama K, Kuwajima H, Moriwaki K, Wada N, Hayashi Y, Yoshioka K. Renal tubular dysgenesis: the first case reported in Japan. *Clin Exp Nephrol* 2001; 5: 197-199.
4. Dreisbach AW, Batuman V. Low-molecular-weight protein competition for binding sites on renal brush border membranes. *Ren Physiol Biochem* 1994; 17: 287-293.

5. Fleming S, Lindop GB, Gibson AA. The distribution of epithelial membrane antigen in the kidney and its tumors. *Histopathology* 1985; 9: 729-739.
6. Bernstein J. Glomerulocytic kidney disease-nosological considerations. *Pediatr Nephrol* 1993; 7: 464-470.
7. Barr M Jr, Sedman AB, Heidelberger KP. Renal tubular dysgenesis in twins. *Pediatr Nephrol* 1998; 12: 408-413.
8. Blythe WB. Captopril and renal autoregulation. *N Engl J Med* 1983; 308: 390-391.
9. Cunniff C, Jones KL, Philipson J, Bunirschke K, Short S, Wujek J. Oligohydramnios sequence and renal tubular malformation associated with maternal enalapril use. *Am J Obstet Gynecol* 1990; 162: 187-189.
10. Metzman RA, Husson MA, Dellers EA. Renal tubular dysgenesis: a description of early renal maldevelopment in siblings. *Ped Pathol* 1993; 13: 239-248.
11. Querfeld U, Ortmann M, Vierzig A, Roth B. Renal tubular dysgenesis: a report of two cases. *J Perinatol* 1996; 16: 498-500.
12. Guron G, Frieberg P. An intact rennin-angiotensin system is a prerequisite for normal renal development. *J Hypertens* 2000; 18: 123-137.
13. Gasparo M, Levens N. Pharmacology of angiotensin II receptors in the kidney. *Kidney Int* 1994; 46: 1486-1491.
14. Grone HJ, Simon M, Fuchs E. Autoradiographic characterization of angiotensin receptor subtypes in fetal and adult human kidney. *Renal Fluid Electrolyte Physiol* 1992; 31: 326-331.
15. Bernstein J, Barajas L. Renal tubular dysgenesis: evidence of abnormality in the rennin-angiotensin system. *J Am Soc Nephrol* 1994; 5: 224-227.
16. Milunsky JM, Genest DR, Milunski A. Renal tubular dysgenesis with microcephaly. *Pediatr Nephrol* 1997; 11: 494-496.
17. McFadden DE, Pantzar JT, Van Allen MI, Langlois S. Renal tubular dysgenesis with calvarial hypoplasia: report of two additional cases and review. *J Med Genet* 1997; 34: 846-848.
18. Kumar D, Moss G, Primhak R, Cooms R. Congenital renal tubular dysplasia and skull ossification defects similar to teratogenic effects of angiotensin converting enzyme (ACE) inhibitors. *J Med Genet* 1997; 34: 541-545.
19. Swinford AE, Brenstein J, Toriello HV. Renal tubular dysgenesis: delayed onset of oligohydramnios. *Am J Med Genet* 1989; 32: 127-132.
20. Russo R, Blackie RA, House MJ. A further family with congenital renal proximal tubular dysgenesis. *J Med Genet* 1990; 27: 395-398.
21. Kriegsmann J, Coerdts W, Kommos F, Beetz R, Hallermann C, Muntefering H. Renal tubular dysgenesis (RTD) – an important cause of the oligohydramnios sequence. Report of 3 cases and review of the literature. *Pathol Res Pract* 2000; 196: 861-865.
22. Scarcella A, Pecararo C, D'Angelo MR, Sole AN. Renal tubular dysgenesis without pulmonary hypoplasia. *Pediatr Nephrol* 1994; 8: 216-217.