2014

Renal Dysplasia

Halana V. Whitehead
Washington University School of Medicine in St. Louis

Renal Dysplasia

Halana Whitehead, M.D.

Overview

Renal dysplasia (RD) is characterized by abnormal differentiation of the nephrons and collecting ducts, decreased nephron number, increased stromal elements and the presence of metaplastic tissues such as cartilage.[1–3] RD is part of a group of disorders known as Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). These disorders represent approximately 70% of pediatric chronic kidney disease.[3] Dyplastic kidneys vary in size and in the presence of cysts. The spectrum of RD ranges from small- or normal-sized kidneys, with or without cysts, to markedly enlarged kidneys with significant cystic changes.[2] An extreme phenotype of RD are multicystic dysplastic kidneys (MCDK). Renal hypodysplasia refers to small dysplastic kidneys without gross cystic changes.[3]

Epidemiology

Unilateral RD occurs in 1 in every 3,000 to 5,000 births and bilateral dysplasia occurs in 1 in every 10,000 births.[1,3] The incidence of CAKUT in general is 0.3 to 1.6 per 1,000 births.[3] Bilateral RD, in particular hypodysplasia, is the most common cause of chronic renal failure in childhood and has been reported to account for 25% of pediatric patients requiring renal replacement therapy.[1,4]

Pathogenesis

The pathogenesis of RD is multifactorial with numerous causes thus far identified including genetic mutations and drug exposures, but in most cases a cause is never identified. In

humans, kidney development begins at 4 weeks gestation in a sequential pattern. Two transient structures, the pronephros and mesonephros, develop prior to the formation of the metanephros. The metanephros is a permanent embryologic structure which develops into the mature kidney. The initial step of metanephric development is the formation of the ureteric bud. This is an out-growth of epithelial cells from the distal aspect of the Wolffian duct. The ureteric bud continues to grow from the reciprocal interactions of the ureteric epithelium and the surrounding metanephric mesenchyme. This reciprocal interaction induces branching morphogenesis in a stereotypic pattern of kidney formation. When the ureteric bud develops in an abnormal location this alters the interaction between the ureteric bud and the metanephric mesenchyme leading to abnormal renal differentiation and RD.[5,6] RD also develops when lower urinary tract obstruction occurs during fetal development. Lower urinary tract obstruction in animal models has caused renal dysplasia, but the cystic changes seen in these models are less prominent. Metaplastic tissues are absent, demonstrating that there are likely additional factors at play in human disease.[1] Studies have also demonstrated an imbalance of cell proliferation and programmed cell death in human RD. Proliferative factors such as PAX2 and BCL2 are overexpressed in cystic epithelia in RD. Dysplastic kidneys have also been shown to have more apoptotic cells than their normal counterparts which may explain the tendency for involution in RD.[6]

Genetics

The majority of human RD occurs sporadically, but some studies have found clustering of renal abnormalities in families of patients with severe RD.[2] The most common renal abnormality seen with a familial pattern is unilateral agenesis, which, given RD's tendency to involute, may represent a history of unilateral RD.[2]

Numerous syndromes are associated with RD and CAKUT, including Beckwith-Wiedemann, DiGeorge, Meckel-Gruber and Fanconi anemia. Of particular interest is an entity known as Renal Cysts and Diabetes (RCAD) syndrome which is caused by mutations in the transcription factor *HNF1b*. RCAD features glucose intolerance or diabetes and renal malformations including RD, polycystic kidneys and solitary kidney. Uterine malformations have been reported in women with RCAD. RCAD can occur secondary to a de novo mutation or inherited in a dominant pattern.[1,6] RCAD may go undiagnosed in families until a child with a more severe renal phenotype is born. Additionally, mutations in the gene encoding *HNF1b* have been seen in patients with prenatally diagnosed renal abnormalities even in the absence of a family history concerning for RCAD.[1]

Additional genes implicated in RD included *PAX2* and uroplakins. *PAX2* has been shown in mouse models to cause renal agenesis in null mutants and renal hypoplasia in heterozygotes. *PAX2* overexpression has been shown to cause RD and cystic changes. PAX2 mutations in humans cause renal-coloboma syndrome andhave also been associated with hypertension.[1] Uroplakins are a group of proteins expressed on the urothelial surface. Uroplakin II and IIIA mutations have been demonstrated in patients with severe RD and uroplakin mutations have also been linked to VUR.[1]

Diagnosis and Clinical Presentation

RD is technically a histologic diagnosis, but can be deduced from imaging, particularly ultrasonography.[2] RD is often first identified on prenatal ultrasonography. CAKUT represent one third of abnormalities detected on routine prenatal ultrasound.[6] A study by Fraser et al. of 53 RD patients in the U.K. reported that 60% were diagnosed by prenatal ultrasonography, with the majority detected during the 20 week anatomic survey.[7]

Features of prenatally diagnosed RD include renal size discrepancy, renal pelvic dilation, and cystic changes.[1,2,7] Dysplastic kidneys can be small or enlarged, although there is likely an early diagnostic bias for enlarged kidneys, which are easier to visualize.[1,2] When one kidney is noted to be abnormal, a careful examination of the contralateral kidney is required as 30-50% will have additional abnormalities.[2] Decreased amniotic fluid volume is associated with severe bilateral disease and often leads to an earlier diagnosis of RD.[1,2] RD may also be associated with lower urinary tract abnormalities. Bilateral MCDK in particular is often associated with ureteric atresia.[2] It is important to note that the renal phenotype can evolve over the course of the pregnancy. Resolution occurs in some cases, but abnormalities may also become more prominent.[1,2]

When there is concern for RD on prenatal ultrasound, a detailed anatomic assessment of the fetus should be performed as one third have abnormalities in other organ systems.[2] Assessment for additional anomalies is also important to evaluate the potential for a multi-organ system genetic syndrome as the cause. Additional abnormalities may determine if chromosomal analysis is indicated.[1,2] Further work-up for prenatally diagnosed RD should include a detailed family history for both renal disease and conditions such as diabetes to assess for inherited causes and risk of disease in future children. Renal ultrasound screening of first-degree relatives should also be considered.[2] Assessment for inherited causes is important both for the fetus's prognosis and for assessing recurrence risk with future pregnancies, which is low in the absence of inherited causes (approximately 2-3%).[2]

When RD is not diagnosed prior to birth, diagnosis often occurs in the neonatal period when an ultrasound is ordered due concerning physical exam findings (abdominal mass, palpable bladder, etc.), laboratory abnormalities (mainly elevated creatinine) or the presence of conditions associated with renal abnormalities which prompt screening.[7] The Fraser et al. study

noted that of the 40% of patients diagnosed postnatally, half came to attention in the neonatal period. Many of the remaining patients presented within the first two years of life with UTI.[7]

Management and Outcomes

The course and prognosis of RD depends primarily on 2 factors: 1) whether the patient's RD associated with a genetic syndrome and 2) whether the RD is unilateral or bilateral. In the case of RD associated with a syndrome, the prognosis is largely dependent on the presence of extra-renal abnormalities such as cardiac and neurologic disease.[1]

In the case of isolated/(non-syndromic) RD, bilateral RD carries a worse prognosis, particularly if it associated with oligohydramnios and poor renal growth or involution in utero. This can lead to pulmonary hypoplasia (Potter's sequence) and many infants die in the neonatal period from respiratory failure. In cases of less severe pulmonary disease, but with poor kidney function dialysis can be considered but is technically difficult in neonates.[1,2] In patients with less severe bilateral RD, the onset of renal failure is usually later, making renal replacement therapy easier to manage and, once a child is 10 kg or greater, renal transplant becomes a therapeutic option.[1,2]

Unilateral RD has a significantly better prognosis, particularly if the contralateral kidney is normal. Most dysplastic kidneys ultimately involute without issue. This results in compensatory hypertrophy of the contralateral kidney. [2] Compensatory hypertrophy may even begin prenatally. In the majority of patients with isolated unilateral disease, renal failure and decreased renal function do not develop, but nearly half have hypertension in adulthood.[2] Historically it was believed that the dysplastic kidney conferred an increased risk of renal tumors, but this has not borne out in more recent studies. As such, elective nephrectomy is no longer recommended unless there is another indication.[1,2]

While prognosis is difficult to determine prenatally, post-natal glomerular filtration rate (GFR) has been shown to have some predictive value. A GFR <15 mL/min per 1.73m^2 at 6 months or <25 mL/min per 1.73m^2 at 18 months has been associated with a worse prognosis, although more recent studies indicate that GFR at age 5 may be more predictive of long-term renal function due to delayed renal growth.[1,2] Additionally, poor postnatal renal growth in both unilateral and bilateral RD, renal scarring and the presence of posterior urethral valves or VUR are associated with poorer outcomes.[7] In cases of RD associated with lower urinary tract obstruction, prognosis cannot be determined until after the obstruction is corrected.[2]

In both unilateral and bilateral RD, referral to a pediatric nephrologist should be made promptly after the diagnosis of RD so that progression and renal growth can be closely monitored. In the case of certain lower urinary tract abnormalities such as vesicoureteral reflux (VUR), antibiotic prophylaxis may be indicated to prevent UTI and subsequent renal scarring.[1] The role of other medications in RD remains unclear. ACE inhibitors and ARBs may help improve long-term renal function in RD, as they do in adults with proteinuric CKD, but this has not been well-studied to date.[2]

References

1. Winyard P, Chitty LS. Dysplastic kidneys. Semin Fetal Neonatal Med [Internet] 2008 [cited 2014 Jul 8];13(3):142–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18065301

2. Winyard P, Chitty L. Dysplastic and polycystic kidneys: diagnosis, associations and management. Prenat Diagn [Internet] 2001 [cited 2014 Jul 16];21(11):924–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11746145

3. Bakkaloglu SA, Schaefer F. Diseases of the Kidney and Urinary Tract in Children. In: Taal, Maarten; Chertow, Glenn; Marsden, Philip; Skorecki, Karl; Yu, Alan SL; Brenner B, editor. Brenner & Rector's The Kidney. Philadelphia, PA: Elsevier; 2012. p. 2622–79.

4. Ardissino G, Daccò V, Testa S, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics [Internet] 2003 [cited 2014 Jul 10];111(4 Pt 1):e382–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12671156

5. Elder JS. Congenital Anomalies and Dysgenesis of the Kidneys [Internet]. In: Kliegman R, Stanton B, St. Gemell J, Schor N, Behrman R, editors. Nelson Textbook of Pediatrics, 19/e. Elsevier Inc.; 2011. p. 1827–9.Available from: http://dx.doi.org/10.1016/B978-1-4377-0755-7.00531-5

6. Woolf AS, Price KL, Scambler PJ, Winyard PJD. Evolving concepts in human renal dysplasia. J Am Soc Nephrol [Internet] 2004 [cited 2014 Jul 8];15(4):998–1007. Available from: http://www.jasn.org/cgi/doi/10.1097/01.ASN.0000113778.06598.6F

7. Fraser N, Paul A, Williams a. R, Broderick N, Shenoy MU. Dysplastic kidneys in children - Do they grow? J Pediatr Urol [Internet] 2010 [cited 2014 Jul 8];6(1):40–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19570721