Congenital Urinary Tract Obstruction: The Long View

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Maldevelopment of the collecting system resulting in urinary tract obstruction (UTO) is the leading identifiable cause of CKD in children. Specific etiologies are unknown; most cases are suspected by discovering hydronephrosis on prenatal ultrasonography. Congenital UTO can reduce nephron number and cause bladder dysfunction, which contribute to ongoing injury. Severe UTO can impair kidney growth in utero, and animal models of unilateral ureteral obstruction show that ischemia and oxidative stress cause proximal tubular cell death, with later development of interstitial fibrosis. Congenital obstructive nephropathy, therefore, results from combined developmental and obstructive kidney injury. Because of inadequacy of available biomarkers, criteria for surgical correction of upper tract obstruction are poorly established. Lower tract obstruction requires fetal or immediate postnatal intervention, and the rate of progression of CKD is highly variable. New biomarkers based on proteomics and determination of glomerular number by magnetic resonance imaging should improve future care. Angiotensin inhibitors have not been effective in slowing progression, although avoidance of nephrotoxins and timely treatment of hypertension are important. Because congenital UTO begins in fetal life, smooth transfer of care from perinatologist to pediatric and adult urology and nephrology teams should optimize quality of life and ultimate outcomes for these patients.

Key Words: Urinary tract obstruction, Child, Chronic kidney disease, Progression, Biomarkers

Congenital anomalies of the kidneys and urinary tract account for most CKD in children, and congenital urinary tract obstruction (UTO) is the leading cause of pediatric end-stage kidney disease.[1] Although complications of diabetes and hypertension are the dominant causes of kidney failure in adults, it is now recognized that in most children requiring kidney replacement therapy for congenital urinary tract anomalies, the onset of kidney failure is delayed until adulthood.[2,3] It is, therefore, appropriate that perinatologists along with pediatric and adult nephrologists and urologists develop an understanding of the natural history of these disorders. This is particularly important as specialty care is transferred from obstetrics to pediatric and then adult nephrologists and urologists. To optimize outcomes, such transitions require close communication and coordination of services throughout the life of the patient.

PATHOGENESIS OF CONGENITAL URINARY TRACT OBSTRUCTION

Factors contributing to maldevelopment of kidneys and urinary tract are poorly understood. Candidate genes have been identified in murine spontaneous congenital hydronephrosis, and knockout mice with a hydronephrotic phenotype have been studied to determine underlying mechanisms.[4] These include abnormalities of ureteral or bladder development and dysfunctional ureteral peristalsis leading to functional (not mechanical) UTO.[5]

Significant advances have been made in understanding the cell and molecular biology of nephrogenesis, and it is now recognized that the number of nephrons per kidney can vary by more than 10-fold in normal individuals.[6] Maturing nephrons adapt to the number of nephrons formed: glomeruli and tubules exhibit compensatory growth when nephrogenesis is terminated before the normal range of nephron number is reached.[7] Human nephrogenesis is complete by 36-week gestation, and additional nephrons are not formed after term birth. Preterm, particularly very low-birth weight infants, are born with low nephron number, and preliminary reports suggest that normal nephrogenesis does not continue postnatally.[8]

Multiple animal models have been developed to unravel the pathophysiology of congenital obstructive nephropathy, which results from the superposition of obstructive kidney injury and developmental injury.[9] Surgical obstruction of the ureter has become the most widely employed animal model of CKD, with kidney interstitial fibrosis serving as the primary end point.[10] We have recently reported that complete unilateral ureteral obstruction (UUO) in the adult mouse results in rapid loss of kidney parenchyma because of a 65% reduction in proximal tubular mass, the result of cell death by necrosis, apoptosis, and autophagy (Fig 1).[11] Progressive tubular atrophy leads to the formation of numerous atubular glomeruli.[12] Complete UUO results in tubular oxidative stress and reduced kidney metabolism and oxygen consumption (largely contributed by proximal tubular cells; Fig 1).[11] It is likely that this is attributable to mitochondrial damage and decreased generation of ATP.[13,14]

Complete UUO in the neonatal mouse also results in tubular oxidative stress, but cell death is delayed until mitochondrial maturation is complete and tubular energy generation has switched from glycolytic to oxidative metabolism.[15] Renin production by the obstructed kidney is markedly increased and is the result of recruitment of renin-producing cells along the afferent arteriole (Fig 1).[12,16] Activation of the intrarenal renin-angiotensin system contributes to tubular and interstitial injury, as demonstrated by a close correlation between injury and

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angiotensinogen gene copy number in transgenic mice.[17] Increased production of angiotensin stimulates the production of transforming growth factor-β, which also contributes to tubular and interstitial injury.[18] With progression of injury, macrophages are attracted to the peributular interstitium, and fibroblasts become activated by releasing cytokines, thus transforming into myofibroblasts, which increase deposition of intracellular matrix.[19,20] Compared with the extent of tubular damage, there is only a modest increase (15%) in interstitial collagen and fibronectin (Fig 1).[11] These findings are consistent with those in kidneys from children with ureteropelvic junction obstruction: proximal tubular mass is often reduced, whereas interstitial injury is limited to 10% to 25% of cases.[21]

Congenital obstructive nephropathy is almost always because of partial rather than complete UTO, and the development of kidney cellular responses is gradual rather than acute. We have, therefore, developed a model of partial UUO in the neonatal mouse or rat, species in which nephrogenesis is not completed until after the third postnatal day.[22,23] This model permits varying the severity, timing, and duration of obstruction; release of the obstruction also permits the study of recovery.[23] Adaptation by remaining nephrons takes place in both obstructed and intact contralateral kidneys, thereby revealing the impact of persistent or transient obstruction on individual nephrons. Impairment of kidney growth is dependent on the severity of obstruction, but this is not a linear relationship: there is a critical luminal diameter below which kidney growth is reduced (Fig 2).[22] This likely explains the poor correlation of kidney pelvic diameter with kidney function in infants with hydronephrosis. It is obviously desirable to ensure that the luminal diameter of the ureter be kept well to the left of the inflection, which provides a rationale for pyeloplasty (Fig 2). After surgical intervention, however, ureteral peristaltic dysfunction and persistently reduced ureteral compliance may limit postoperative functional recovery.

It should be noted that most of the increase in kidney parenchymal mass in infancy is a reflection of proximal tubular growth (both proliferation and hypertrophy).[24] Nephron damage after neonatal partial UUO, although progressing more slowly than when following complete obstruction, is also characterized by proximal tubular apoptosis and necrosis, leading to glomerulotubular disconnection and the formation of atubular glomeruli.[23] Although release of obstruction arrests progression of the proximal tubular lesion and is followed by remodeling of the kidney architecture, glomerular growth remains impaired.[23] In neonatal rats with variable partial UUO, the rate of compensatory growth of the contralateral (nonobstructed) kidney is dependent on the severity and duration of obstruction and takes place at the single nephron level.[25] In neonatal mice, there is enhanced growth of the proximal tubule and a reduction of interstitial collagen in the nonobstructed contralateral kidney after the release of partial UUO.[26] These responses are likely the result of oxidative stress, which increases in both kidneys after UUO and decreases after the release of obstruction.[15] Although fine-tuning of compensatory growth of the contralateral kidney is detectable in inbred rodents, biologic variation in man along with limitations in measurement of kidney size diminish the utility of such measurements in predicting the function of the obstructed kidney as proposed previously.[27,28]

In addition to impaired nephrogenesis resulting from (or associated with) UTO, the risk for reduced nephron number is compounded in affected preterm and intrauterine growth-restricted infants. This concern has grown from epidemiologic studies by Barker and his group, which linked low birth weight to adult cardiovascular disease, an association that has been extended to CKD. Low nephron number is also associated with low birth weight, and it is now becoming clear that nephron endowment at birth is a strong determinant of kidney health throughout the life cycle.[6,29,30] To determine the role of nephron number in the progression of congenital obstructive nephropathy, mutant mice with 50% reduction in nephron number were compared with wild-type mice subjected to transient partial UUO.[26] In contrast to mice with normal nephron number, nephron growth in mice with congenital nephron deficiency was not restored after release of UUO, and there was additional nephron loss.[26] This suggests that low-birth weight infants with congenital UTO are likely to be at increased risk for progression and to have limited recovery after surgical correction of obstruction.

CLINICAL SUMMARY

- Congenital urinary tract obstruction impairs kidney growth and development, dependent on the severity, duration, and timing of obstruction.
- The primary objectives in management of upper tract obstruction are selection of appropriate candidates for surgical correction and optimal timing of the operation.
- The primary objective in management of lower tract obstruction is to relieve the obstruction as soon as feasible; generally, in the immediate postnatal period (fetal intervention carries significant risk to mother and fetus).
- Medical therapy to slow progression of CKD in children with obstructive nephropathy is limited, and angiotensin inhibitors must be used with caution in infants because of their interference with normal kidney development.
- Regardless of surgical intervention, long-term outcomes are optimized by smooth transition of care from perinatologist to pediatric and adult nephrologist and urologist.

CLINICAL PREDICTORS OF PROGRESSION IN CONGENITAL URINARY TRACT OBSTRUCTION

It is ironic that, at the present time, there is no generally accepted definition of congenital UTO. Peters[31] has proposed: "Obstruction is a condition of impaired urinary drainage which, if uncorrected, will limit the ultimate functional potential of a developing kidney." Although this definition rightly emphasizes the importance of