Variable chronic partial ureteral obstruction in the neonatal rat: A new model of ureteropelvic junction obstruction

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Background. Congenital ureteropelvic junction (UPJ) obstruction is a common developmental anomaly. To elucidate the mechanisms underlying the renal consequences of congenital UPJ obstruction, we have developed a new model of variable partial unilateral ureteral obstruction (UUO) in the neonatal rat.

Methods. Rat pups were subjected to sham-operation, complete UUO, or variable partial UUO within the first day of life. After 14 or 28 days, the relative number of glomeruli, cell proliferation, tubular apoptosis, tubular atrophy, and interstitial fibrosis were quantitated in histologic sections. Glomerular filtration rate (GFR) was determined after 28 days of partial or complete UUO.

Results. Following 70% to 75% reduction in ureteral diameter, renal growth from 14 to 28 days was reduced by 60%, and the number of glomeruli decreased by 50%. Renal pelvic diameter increased in proportion to the severity of obstruction following 14 days of partial UUO, and by 28 days, was maximally dilated regardless of the luminal diameter. Renal proliferation was increased, while tubular apoptosis, tubular atrophy, and interstitial fibrosis were less severe 14 days following partial UUO than in complete UUO. GFR was reduced by 80%, and proteinuria developed following 28 days of partial UUO.

Conclusion. Renal function is impaired by chronic ipsilateral partial UUO, which reduces the number of nephrons, and leads to progressive renal pelvic dilatation. Tubular atrophy and interstitial fibrosis develop prior to significant renal pelvic dilatation. Correlation of clinically measurable parameters with renal morphometry or imaging studies in this model may lead to new approaches to the management of congenital UPJ obstruction.

Key words: obstructive nephropathy; renal growth, apoptosis, glomerular number.

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is a broad spectrum of severity of obstruction among individual patients, and the natural history of the lesion remains incompletely understood [3]. At one end of the spectrum, mild ureteral stenosis causes no long-term renal injury or reduction in renal function. At the other end, severe stenosis of the UPJ early in nephrogenesis impairs renal growth and development, such that even prompt surgical repair does not result in significant recovery of renal function. Most patients fall between these two extremes, however, and there is considerable disagreement regarding the ultimate prognosis or the indications and timing of surgical repair. The currently available diagnostic evaluation comprises prenatal and postnatal sonography, as well as postnatal diuretic renography. Renal histologic study of infants with severe UPJ obstruction reveals glomerular sclerosis, tubular atrophy, and interstitial fibrosis [4–7]. More recently, potential urinary biomarkers of obstructive nephropathy have been identified, including epidermal growth factor (EGF) and transforming growth factor-beta (TGF-β) [8, 9]. These were discovered on the basis of animal models of obstructive nephropathy, which revealed significant changes in growth factor expression [10].

A number of animal models have been developed to study the pathophysiology of congenital hydronephrosis. These include ureteral obstruction in the fetal sheep, as well as in the postnatal opossum, pig, rabbit, and rodent [10–14]. We have examined the renal cellular and functional consequences of complete unilateral ureteral obstruction (UUO) in the neonatal rat and mouse, which bear many similarities to human obstructive nephropathy [15, 16]. However, since most UPJ obstruction is partial rather than complete, models of partial UUO would appear to better mirror the clinical spectrum of disease. We have previously reported the consequences of partial UUO on the kidney of the neonatal guinea pig, a species in which nephrogenesis, like the human, is complete before birth [17–19]. However, since the UPJ lesion in humans develops in utero (during nephrogenesis), a better model may be the surgical induction of partial UUO in the neonatal rat. Josephson et al [20, 21] reported a series

1See Editorial by Peters, p. 371.
of studies of the renal consequences of partial UUO in the neonatal rat, with the obstruction induced by burying one ureter in the psoas muscle. This resulted in a mild variable hydronephrosis and minimal reduction in glomerular filtration rate (GFR).

We wished to develop a model of chronic partial UUO in the neonatal rat, in which it would be possible to adjust the severity of obstruction, and to determine both the short-term and long-term renal consequences of obstruction. Our goal was to characterize such a model with respect to renal structural and functional outcome. This may lead to the development of new biomarkers of obstruction and medical or surgical interventions that can then be tested in clinical series.

METHODS

Animal surgery

Twenty-four to 48 hours following birth, rat pups were removed from their mother for surgery. Each pup was weighed and anesthetized with isoflurane and oxygen. All surgery was performed under sterile technique, and there was no histologic evidence of pyelonephritis in any of the animals with partial or complete UUO. Antibiotics were not used in the study, as potential nephrotoxicity could complicate interpretation of the results. The left ureter was exposed through a flank incision, a 3 mm length of stainless steel wire (T-304V) (Small parts Inc., Miami, FL, USA) was placed adjacent to the ureter, and a ligature of 8-0 nylon was tied around both ureter and template at the UPJ. Care was taken by the surgeon to use the same degree of tension to tie each ligature. A nonslip double cast was made initially, such that the knot was completely closed, but not stretched around the wire template. A second single cast completed the square knot, but was again not stretched. A third, locking cast was finally added and tightened to guarantee the security of the knot without affecting the tension on the loop. The same investigator performed all of the operations in this study. The wire was then removed, leaving the ligature around the ureter. Wire diameters of 0.25, 0.30, and 0.35 mm were used. In additional animals, wire diameters of 0.60 and 0.95 mm were used. Diameters of 0.25 or 0.30 mm created severe obstruction, 0.35 mm created moderate obstruction, and 0.60 or 0.95 mm created mild obstruction. The incision was closed in a single layer with 6-0 polypropylene suture and coated with tissue cement. Complete UUO was created in additional rat pups by ureteral ligation. Sham-operated pups underwent the same surgical procedure, except that the ureter was left intact. Animals were allowed to recover on a warming pad, then returned to their mother.

As shown in Figure 1A, partial UUO resulted in hydronephrosis and pelvic dilatation. When India ink was injected into the pelvis, it flowed past the obstruction. As shown in Figure 1B, the nylon suture material did not elicit a significant inflammatory response around the ureter. The severity of hydronephrosis was directly related to the severity of partial obstruction (Fig. 1C). At the time of sacrifice, before removal of the kidneys, the diameter of the renal pelvis and of the ureter proximal to the obstruction was measured with calipers.

Tissue processing

After 14 or 28 days, animals were sacrificed by sodium pentobarbital injection, and kidneys were removed for histologic study. Kidneys were fixed for 24 hours in 10% buffered formalin, embedded in paraffin, and sectioned at 4 μm as described previously [15]. The total number of glomeruli per sagittal section was determined using periodic acid-Schiff (PAS)-stained sections, a technique that has been validated by comparison with the stereologic disector technique [22]. Atrophic tubules were identified by thickened tubular basement membranes and quantitated as described previously [15]. Relative interstitial fibrosis was quantitated in sections stained with picrosirius red stain using image analysis software (Image Pro Plus, Media Cybernetics, Silver Spring, MD, USA) [15]. Proliferating cells were identified using monoclonal mouse antirat proliferating cell nuclear antigen (Vector Laboratories, Burlingame, CA, USA) as described previously [23], and were quantitated using image analysis. Apoptotic cells were identified using the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate (dUTP)-biotin nick end labeling (TUNEL) technique (Apoptag) Serologicals, Inc., Norcross, GA, USA) and were quantitated as described previously [24]. Selected animals were perfused with glutaraldehyde and sections of their kidneys were plastic-embedded for detailed light microscopic examination, as described previously [25].

Renal function studies

Twenty-eight days following partial or complete UUO or sham operation, additional rats were anesthetized with isoflurane and oxygen, and placed on a thermostatically controlled heating table. Left and right ureters were cannulated with PE-10 tubing inserted such that the tip was placed immediately distal to the obstruction. Urine was collected into preweighed tubes containing 100 μL distilled water. Three 20-minute collections were obtained following 1 hour of equilibration. The results were averaged for the three collections. Infusion of 3H inulin and replacement of blood samples with 4% bovine serum albumin (BSA) were performed as described previously [15]. Urine protein concentration was measured by the Amidoschwartz method as described previously [16].

Statistical analysis

Data are presented as mean ± standard error. Comparisons between groups were made using one-way analysis
of variance (ANOVA) followed by the Student-Newman-Kuels test. Comparisons between left and right kidneys were performed using the Student t test for paired data. Statistical significance was defined as $P < 0.05$.

RESULTS

As shown in Figure 2, somatic growth was not affected by partial UUO in the first 2 weeks of life, but by the third and fourth weeks, body growth was impaired proportional to the severity of obstruction. By 28 days of age, body weight of rats subjected to 0.25 mm partial obstruction was lower than that of sham-operated rats ($P < 0.05$). After 14 days, kidney weight was not affected by ipsilateral UUO (Fig. 3A). However, after 28 days, kidney growth was impaired in the obstructed kidney in proportion to the severity of obstruction ($R = 0.73, P < 0.001$) (Fig. 3A and C). Variability in kidney weight was greater
in sham and partial UUO kidneys than in complete UUO (Fig. 3C). As shown in Figure 3D, interval renal growth from 14 to 28 days was reduced with increasing severity of obstruction (luminal diameter of the unobstructed ureter is 1 mm). The impairment of renal growth was not a linear function of the degree of ureteral stenosis: there was only a 20% reduction in the rate of renal growth with a 0.35 mm partial obstruction, but there was a 66% reduction with stenosis of 0.30 or 0.25 mm. Complete ureteral obstruction prevented any renal growth between 14 and 28 days of age. While the severity of partial UUO had no effect on growth of the intact opposite kidney at either 14 or 28 days, complete UUO resulted in significant additional contralateral renal growth at both 14 and 28 days (Fig. 3B).

As shown in Figure 4A and B, there was a progressive increase in renal pelvic diameter at 14 days, proportional to the degree of obstruction \((R = 0.74, P < 0.001)\). By 28 days, renal pelvic diameter was similar for all three degrees of partial ureteral constriction (Fig. 4A). There was greater variability in pelvic diameter with increasing severity of obstruction (Fig. 4B). Ureteral diameter proximal to the obstruction paralleled the changes in the renal pelvis. By 14 days of obstruction, the ureter was dilated for the most severe (0.25 mm), but not for the less severe degrees of obstruction (Fig. 4C). By 28 days, obstruction of 0.35, 0.30, or 0.25 mm resulted in significant dilatation of the ureter (Fig. 4C). In additional groups of neonatal rats subjected to mild degrees of partial UUO (0.95 mm or 0.60 mm), ureteral dilatation did not develop until 42 days of obstruction (Fig. 4D).

Following 14 days of complete UUO, the number of glomeruli decreased by over 50%, but no significant reduction in glomeruli occurred in kidneys subjected to either 0.30 or 0.35 mm partial obstruction (Fig. 5A). However, following 28 days of partial UUO, the number of glomeruli was reduced by 50%, a level similar to that of the completely obstructed kidney (Fig. 5B). In contrast, UUO had no effect on the number of glomeruli in the intact opposite kidney (Fig. 5). Histologic examination of the kidneys following 14 days of partial UUO did not reveal glomerular sclerosis. However, numerous atypical glomeruli were detected, containing compressed capillaries, poorly differentiated epithelial cells, and an indistinct Bowman’s capsule (Fig. 6A and B).

As shown in Figures 6C and 7A, 0.35 mm partial UUO induced an increase in cellular proliferation in the ipsilateral kidney, whereas more severe partial obstruction (0.30 mm) or complete UUO did not increase proliferation compared to sham-operated rats (Fig. 7A). Conversely, there was no effect of either 0.30 or 0.35 mm partial UUO on renal tubular apoptosis, whereas complete UUO resulted in a fivefold increase in apoptosis (Figs. 6D and 7B). The impact of 0.30 mm partial UUO (but not 0.35 mm obstruction) on tubular atrophy and interstitial fibrosis at 14 days was also less than that in rats with complete UUO, but greater than that in sham-operated animals (Figs. 6E and F and 7C and D). In the kidneys contralateral to partial or complete UUO, none of these parameters was affected.

Urine flow rate was similar in partially obstructed and intact contralateral kidneys, and was not different from that of sham-operated rats (Fig. 8A). However, glomerular filtration rate was reduced by 80% following 28 days of partial UUO (Fig. 8B). Urine protein excretion from the partially obstructed kidney was increased compared to that of the sham-operated or contralateral kidney (Fig. 8C). Urine protein excretion was even greater from the kidney contralateral to complete UUO (Fig. 8C).

**DISCUSSION**

This study represents the first investigation of a model of variable partial UPJ obstruction in the neonatal rat. The major advantages of this model are the reproducibility of the obstruction, the lack of injury to the ureter at the point of stenosis, and the possibility of making serial measurements.

Comparing kidney weight at 28 days to 14 days, renal growth in this interval was 0.35 mg in sham-operated rats (Fig. 3D). In contrast, renal growth was 0.28 mg for 0.35 mm obstruction, only 0.12 mg for 0.30 or 0.25 mm obstruction, and there was no interval growth with complete obstruction (Fig. 3D). These results indicate that renal growth in this interval is minimally impaired by a 65% reduction in luminal diameter, whereas a 70% to 75% reduction in luminal diameter reduces the rate of renal growth by 60%. Thus, rather than there being a linear relationship between renal growth and the severity...
of ureteral obstruction, there instead appears to be a critical threshold below which renal growth is severely impaired. We have shown previously that impairment of renal growth is directly dependent on the duration of temporary complete UUO in the neonatal rat [26]. Moreover, temporary complete UUO applied after nephrogenesis is complete (but while nephron maturation is occurring) impairs renal growth more severely than does temporary complete UUO during nephrogenesis in the neonatal rat [22]. This may relate to apoptotic tubular injury from dilatation secondary to ongoing filtration by more mature nephrons in the older animals. Following this line of reasoning, more severe tubular dilatation in the most severe chronic partial UUO would be expected to cause more tubular apoptosis and eventual tubular atrophy than would the more mild degrees of obstruction. In the neonatal guinea pig, growth of the kidney is impaired as a consequence of severe partial UUO from 3 to 8 weeks of age [27]. However, following release after 10 days partial UUO in the neonatal guinea pig, renal growth is not restored even after 6 weeks of recovery [17]. These observations underscore the susceptibility of the maturing kidney to either partial or complete UUO, either during or after completion of nephrogenesis.

It is important to note that measurements of wet kidney weight reflect changes in renal mass, and not merely tissue water content. Our previous studies of partial UUO in the 23-day-old guinea pig revealed no differences in the effects of dry vs. wet kidney weight regardless of the severity of the obstruction [18]. We have reported that in the neonatal rat subjected to complete UUO at birth, the magnitude of changes in kidney DNA content closely parallel the changes in wet kidney weight [10]. We have also shown previously that changes in dry kidney weight parallel wet kidney weight for neonatal rats subjected to complete UUO at either 1 day or 14 days of age [22]. We conclude therefore that wet kidney weight in these models serves as an accurate reflection of renal growth.

The present study shows that whereas complete UUO reduces the number of glomeruli by approximately 50% after 14 days of obstruction, the loss of glomeruli resulting from partial UUO is more gradual, and continues between 14 and 28 days of obstruction. We have demonstrated that loss of glomeruli from temporary complete
UUO in the neonatal rat is dependent on the duration of obstruction. Five days’ obstruction reduces the number of glomeruli by 50%, whereas 2 or 3 days’ obstruction has a minor impact [22]. Previous studies of partial UUO in the neonatal rat induced by wrapping the ureter in the psoas muscle revealed a 20% reduction in the number of glomeruli and a 10% to 40% reduction in GFR after 9 to 15 weeks [20, 21]. Partial UUO in the neonatal pig results in a 28% reduction in the number of glomeruli [13]. The mechanism of nephron loss due to UUO remains incompletely understood, but may involve both disordered nephrogenesis and destruction of previously formed nephrons. Since nephrogenesis in the rat is complete by 14 days postnatally, the nephron loss observed between 14 and 28 days of partial UUO would therefore result from loss of previously formed glomeruli rather than incomplete nephrogenesis. The glomeruli shown in Figure 6A and B suggest that cellular transformation may account for the disappearance of glomeruli, with differentiated glomerular cells assuming mesenchymal characteristics [28]. Ureteral obstruction in the fetal monkey results in podocyte apoptosis, as well as apoptosis of collecting duct cells [29]. It should be noted that a number of reports of clinical UPJ obstruction demonstrate obsolescent and sclerotic glomeruli, which presumably represent ongoing destruction of nephrons [4–7, 30].

Since the present study indicates that partial UUO leads to progressive ureteral and pelvic dilatation, serial ultrasound examinations should be considered in infants with pelvic dilatation, even if diuretic renography initially shows normal differential renal function. However, there may be a significant reduction in renal function even with maintenance of renal growth. In our model, GFR was reduced by 80% and proteinuria had developed following 28 days partial UUO, despite normal kidney weight and only mild pelvic and ureteral dilatation. Proteinuria presumably resulted from glomerular changes described above.

There remains considerable disagreement regarding the clinical criteria for pathologic pelvic dilatation. Based on a survey of over 34,000 fetal ultrasound examinations, Grignon et al [31] developed a classification of urinary tract dilatation in fetuses with hydronephrosis. Grades III, IV, and V appear to correlate closely with the results of graded partial UUO in our model (Fig. 1C). Since in the present study even animals with mild stenosis developed...
progressive pelvic dilatation, the timing of serial pelvic measurements may be more critical than random ones [32]. In studies of infants with obstructive hydrenephrosis, renal pelvic diameter at 6 weeks of age permitted a much sharper cutoff for defining obstruction than did measurements at 6 days, indicating that obstruction may be underestimated or missed in early studies [33]. Following partial UUO in the neonatal rat, the quantity of renal interstitial collagen deposition is directly correlated with the degree of renal pelvic distention [34]. Although renal interstitial fibrosis in the present study was significantly less with partial than complete UUO, it is likely that with progressive hydrenephrosis, the changes would progress as demonstrated in human studies [4–6]. Of interest, interstitial fibrosis emerged as a highly significant correlate of differential renal function in children with UPJ obstruction, and was significantly related to episodes of superimposed urinary tract infection [7].

In the present study, renal tubular apoptosis was significantly stimulated by UUO, with a markedly greater response in complete as compared to partial obstruction. The impact of apoptosis on renal function following less severe partial obstruction may be abrogated by a greater proliferative response (Fig. 7A). The close parallel of tubular atrophy with apoptosis is consistent with the growing evidence that apoptosis is a major factor in the genesis of hydrenephrotic tubular atrophy, as originally proposed by Gobe and Axelson [35]. The latter may develop from apoptosis of distal nephron segments secondary to tubular stretch, and necrosis of proximal segments due to relative ischemia and hypoxia [36]. Tubular apoptosis is found also in human fetuses and infants with obstructive nephropathy [37, 38].

In the present study, urine flow rates were preserved by the partially obstructed kidney despite an 80% reduction in GFR. Urine flow rates are likely important in determining the functional impact of a given severity of partial obstruction. In weanling rats with partial UUO, chronic high urine flow rates lead to a significant decrease in GFR [39]. There is evidence that in children with UPJ obstruction, periods of diuresis may be associated with kinking of the ureter and intermittent acute complete obstruction [40]. A key question that remains to be answered is the rate of reduction in GFR in relation to the severity of ureteral obstruction. While diuretic renography remains the standard for determining relative renal function in patients with unilateral obstruction, numerous variables limit its accuracy [41]. Following 24 weeks of partial UUO in the neonatal rat created by insertion of the ureter in the psoas muscle, renal blood flow is lower for severe than for mild obstruction, but there is no additional deterioration after 6 weeks [42]. In neonatal pigs subjected to partial UUO by the psoas muscle technique, there is poor correlation of long-term GFR of the obstructed kidney with relative GFR contribution at 4 weeks of age [43]. Severe partial UUO in the neonatal guinea pig leads to renal vasoconstriction, and a drop in filtration fraction associated with a decrease in the ultrafiltration coefficient [18, 19].

Given the presence of a normal contralateral kidney, it is difficult to attribute the mild slowing in somatic growth of neonatal rats with severe partial UUO to a reduction in GFR (Fig. 2). However, functional renal tubular defects have been demonstrated in children with unilateral or bilateral obstructive nephropathy, resulting in abnormal renal concentration or acidification [44]. It has been proposed that the combination of high endogenous acid production and immature compensatory mechanisms can explain the systemic manifestations of renal tubular acidosis in children with unilateral lesions [44]. The deleterious effects of renal tubular acidosis on somatic growth are well described, and may contribute to the findings in the present study.
Compared to the marked response following complete UUO, the lack of compensatory growth of the intact opposite kidney following 4 weeks of severe partial UUO is of particular interest. We have demonstrated that adaptive growth of the opposite kidney is finely tuned to the duration of transient complete UUO in the neonatal rat. Fourteen days after release of complete UUO of 2 to 5 days' duration, the contralateral kidney manifests compensatory growth [26]. Using the insertion of the ureter in the psoas muscle, others have shown that partial UUO in the neonatal rat does not induce contralateral renal growth until after 4 weeks of observation [42]. Interestingly, following three weeks of severe partial UUO in the neonatal guinea pig, the rate of growth of the contralateral kidney increases by 30% (40% after 8 weeks) [27]. Koff et al [45] postulated that monitoring the rate of growth of the intact opposite kidney in children with unilateral UPJ obstruction could be used as a predictor of progressive impairment of the obstructed kidney. However, this has proved difficult because of inaccuracies in sonographic renal measurement, and was not confirmed by others [46]. If the partial UUO is delayed to 14 days of age in the pig, contralateral renal compensatory growth can be detected as early as 4 weeks later [47]. This suggests that the response of the contralateral kidney varies with maturation. Following complete UUO in the midtrimester fetal sheep, the contralateral kidney does not manifest compensatory growth 35 days later, although significant adaptive growth is evident after 75 days [48]. This finding is consistent with a more sluggish adaptive response of the immature kidney to contralateral UUO. It is likely that each kidney releases...
CONCLUSION

There are several significant clinical implications of the study: (1) renal growth is impaired by a critical degree of partial UUO (the relationship is not linear); (2) persistent partial UUO progressively reduces the number of nephrons during the period of nephron maturation (after the completion of nephrogenesis); (3) a fixed partial UPJ obstruction leads to a progressive dilatation of the renal pelvis and proximal ureter; (4) tubular atrophy and interstitial fibrosis are correlated with tubular apoptosis, and develop before detectable pelvic dilatation; (5) persistent moderate partial UUO leads to a marked reduction in ipsilateral GFR and increased protein excretion, before significant impairment of renal growth; (6) compared to complete UUO, partial UUO has a delayed stimulatory effect on adaptive growth of the contralateral kidney; and (7) partial neonatal UUO can impair somatic growth.

This new model of finely variable partial UUO in the neonatal rat has a number of advantages over previously reported techniques. These include (1) study of the impact of varying severity of partial UUO during the period of nephrogenesis, as well as during nephron maturation; (2) study of the impact of duration of variable partial UUO on renal structure and function; and (3) correlation of clinically measurable parameters (pelvic and ureteral diameter, GFR, and tissue or urinary biomarkers) with renal morphometry or imaging studies. The model should advance investigation of new diagnostic and therapeutic approaches to the management of congenital obstructive nephropathy.

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Fig. 8. (A) Urine flow rate for each kidney of neonatal rats 28 days after being subjected to sham operation, partial unilateral ureteral obstruction (UUO) (0.35 mm lumen), or complete UUO within the first 48 hours of life. (B) Glomerular filtration rate for each kidney of same animals. (C) Urine protein excretion of same animals (N = 6 to 8 animals each group; (●) left or obstructed kidney; (□) right or contralateral kidney. *P < 0.05 vs. sham.

a signal that inhibits growth of the contralateral kidney, and that the magnitude of the signal is related to the remaining renal mass. There may be a threshold for release of the inhibitory signal for compensatory growth of the contralateral kidney similar to that shown in the present study for suppression of normal growth of the ipsilateral kidney. Proteinuria in 28-day-old rats subjected to complete UUO presumably resulted from hyperfiltration by glomeruli in the intact kidney that had undergone compensatory growth.