Congenital Obstructive Nephropathy : From the Fetus to the Future

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1. Overview

Obstructive nephropathy is a major cause of renal insufficiency and renal failure in infancy. Diagnosis of congenital obstructive nephropathy by ultrasonography is made increasingly in the prenatal period. The major challenges in prenatal diagnosis are the relatively advanced stage of nephrogenesis at which kidneys are detectable by ultrasound (18 weeks), the difficulty in identifying an abnormally dilated collecting system, and the determination of renal functional status in the fetus. The anteroposterior diameter of the fetal renal pelvis in the second trimester can provide an index of urinary tract obstruction : a value of 5-10 mm should be confirmed by subsequent ultrasound examination.

2. Clinical studies

In two large clinical studies totaling over 10,000 screened fetuses, 2% were found to have hydronephrosis : of those with renal pelvic dilatation, 21% had significant renal abnormalities requiring follow-up. Interpretation of indices of renal functional impairment determined by fetal urine sampling is also problematic : sodium, chloride, total protein, osmolality, $\beta 2$ microglobulin, and N-acetyl-β-D-glucosaminidase have been studied. While reliability of these is variable, sequential determinations appear to be of value. Examination of urine amino acids by nuclear magnetic resonance may offer better discrimination of infants with poor renal functional outcomes. For fetuses older than 20 weeks gestation with severe urethral obstruction, renal histologic study reveals arrested nephrogenesis, myelofibroblastic differentiation of nephrogenic blastema, and α-smooth muscle actin expression by interstitial mesenchyme surrounding primitive ducts, all findings suggestive of changes unlikely to respond to surgical intervention. The outcome of prenatal intervention for bladder outlet obstruction is variable, and difficult to quantitate.

3. UPJ obstruction

Equally controversial at this time is early postnatal pyeloplasty for congenital ureteropelvic junction (UPJ) obstruction. In unilateral UPJ obstruction, interpretation of nuclide renography is problematic, and operation may not improve outcome. Infants with very poor function on renography have advanced glomerular and tubulointerstitial changes and little postoperative improvement, although there is poor correlation of biopsy findings and renography in 25% of patients. Based on the concept of renal counterbalance, serial measurement of growth of the kidney opposite unilateral UPJ obstruction has been suggested as a means of detecting functional impairment of the obstructed kidney. Although infants with bilateral UPJ obstruction can demonstrate compensatory renal growth, long-term follow-up of children with obstructive nephropathy reveals tubular

defects, such as renal tubular acidosis and renal concentrating defects, even in children with unilateral hydronephrosis.

4. Experimental study

We have performed a series of studies in the rodent to elucidate the renal response to unilateral ureteral obstruction (UUO) in early development. Temporary UUO in the neonatal rat impairs renal growth in direct proportion to the duration of obstruction, with a precisely balanced compensatory growth by the intact opposite kidney. Proliferation of renal tubular cells is reduced, and apoptosis is increased in the obstructed neonatal kidney. Only 5 days of UUO followed by release of obstruction reduces the number of glomeruli by 40% but glomerular filtration rate is maintained at one month. Thus, after one month of recovery, measurement of GFR does not appear to correlate with underlying renal damage. However, one year after relief of obstruction, GFR of the postobstructed kidney is reduced by 80% and there is glomerular sclerosis, tubular atrophy, and interstitial fibrosis in both kidneys.

5. Conclusions

We conclude that urinary tract obstruction in the developing kidney results in a complex sequence of cellular responses that leads to impaired renal development and interstitial fibrosis. There are a number of parallels between the renal response to UUO in the neonatal rodent and congenital obstructive nephropathy in the human. Currently, diagnosis and treatment of intrauterine hydronephrosis are difficult. The criteria for prenatal intervention for bladder outlet obstruction are not clear, given the generally disappointing results of fetal surgery. However, delay of pyeloplasty in infants with significant UPJ obstruction may not be justified either, in view of the experimental studies suggesting nephron loss resulting from UUO. Improved understanding of the cellular mechanisms underlying congenital obstructive nephropathy may lead to improved diagnostic and therapeutic approaches in the future.