Obstructive Nephropathy in Children: Long-Term Progression After Relief of Posterior Urethral Valve

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ABSTRACT. *Background.* **Approximately one third of children with end-stage renal disease have the illness because of urinary tract malformations, obstructive uropathy, and hypoplasia/dysplasia. The significant drop in infant mortality from obstructive uropathies in recent decades, attributable to prenatal diagnosis with renal ultrasonography and coordinated surgical and medical care, necessitated a reevaluation of the long-term outcome.**

Methods. **To that end, we examined the long-term progression of obstructive nephropathy after neonatal relief of posterior urethral valves in our center over a span of 21 years, with diagnosis and care being provided by the same pediatric and urology team.**

Results. **The 10 consecutive cases of posterior urethral valves represented 7% of all patients with congenital malformative uropathies seen over this period. The following procedures were performed: primary valve ablation (90%) and vesicostomy (40%). Seventy percent of patients progressed to end-stage renal disease over a (mean ± standard error of the mean) follow-up of 11.3 ± 2.1 years. The linear plot of the log of the inverse of serum creatinine versus time suggested unrelenting progression. The rate of progression was rapid after serum creatinine exceeded 5 mg/dL but the rate was slow and steady from serum creatinine of 1.5 to 5 mg/dL.**

Conclusions. **To test the effect of a therapeutic intervention to ameliorate the rate of progression, this steady and prolonged progression of 0.5 mg/dL per year between serum creatinine concentration of 1.5 to 5 mg/dL would seem the optimal study. *Pediatrics* 2001;107:1004–1010; *posterior urethral valve, obstructive nephropathy, progression.***

ABBREVIATION. ESRD, end-stage renal disease.

Urinary tract malformations, obstructive uropathy, and hypoplasia/dysplasia account for 36% of children with chronic renal failure worldwide.[1] In view of the fact that end-stage renal disease (ESRD) costs the United States a staggering $15.64 billion ($11.76 billion federal costs),[2] and with children accounting for ~10% of the dialysis/transplant population,[3] it seems that the consequences of congenital malformations of the urogenital tract is an issue of great importance in terms of cost to the pediatric health care budget and to the well being of the patients and their families. We wish to share a 21-year experience at a single center with care provided by the same medical team, to examine data on the long-term progression of obstructive nephropathy after neonatal relief of posterior urethral valves.

This study has particular relevance in the light of a recent report demonstrating unrelenting progression of bilateral glomerular and tubular interstitial fibrosis after relief of temporary (5 days) of unilateral ureteral obstruction in neonatal rats followed for 12 months.[4] Thus, the question of whether the advancing technology resulting in neonatal relief of posterior urethral valvular obstruction delays or prevents unrelenting progression of renal disease in the child becomes particularly important.

METHODS

Between January 1978 and December 1999, 10 consecutive pediatric cases of obstructive uropathy from posterior urethral valves were diagnosed and treated at the Medical College of Virginia Hospitals, a regional health care center in the mid-Atlantic area. With 1 exception, all patients were diagnosed and medical care provided under the direction of the same pediatric nephrologist (J.C.M.C.). This is highly selected from a larger group of patients with obstructive uropathy seen by others in our group who did not reach chronic renal failure. The diagnosis of obstructive uropathy was made by ultrasound and posterior urethral valves were confirmed by voiding cystourethrogram and/or cystoscopy. The race, age of valve ablation or vesicostomy, and other clinical characteristics of the 10 children are summarized in Table 1. All patients were identified prenatally by ultrasonography.

Statistical Analysis

In these 10 patients considered here, the observed time from the nadir of serum creatinine after surgery to serum creatinine values of 1.5, 2.5, 5.0, and 7.5 mg/dL were calculated. In some cases, the event had not yet occurred that resulted in a censored observation. From time of the nadir serum creatinine after relief of posterior urethral valve to serum creatinine of 1.5 mg/dL, there were no censored observations; to 2.5 mg/dL, there was 1 censored observation; to 5.0 mg/dL, there were 2 censored observations; to 7.5 mg/dL, there were 5 censored observations; thus, in all cases except time to serum creatinine of 7.5 mg/dL, the median time to the event could be calculated and was unaffected by the censoring. For time to serum creatinine of 7.5 mg/dL, the median is underestimated. Table 2 contains the medians calculated from the data using JMP (SAS Institute, Inc, Cary, NC).[5]

The rates reported in the text were calculated from the entries in Table 2 by considering the change in serum creatinine divided by the difference in median time ($\Delta Cr/\Delta t$) required for the change in serum creatinine.

RESULTS

The presenting symptoms were as follows (Table 1): failure to thrive (100%), weak urine stream (60%),

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TABLE 1. Clinical Characteristics of 10 Children With Posterior Urethral Valves Causing Obstructive Uropathy Seen at Medical College of Virginia Hospitals From 1978 Through 1999

Patient	Race	Prenatal Ultrasound	Failure to Thrive	Weak Urine Stream	UTI	HBP	Kidney Mass	Nadir BUN Postsurgery (mg/dL)	Nadir Cr Postsurgery (mg/dL)	Age at Primary Valve Ablation and Vesicostomy
1	W	+	+	+	+	−	−	22	0.9	1.0
2	W	+	+	+	+	−	−	11	0.5	0.58
3	W	+	+	−	+	−	−	17	0.5	0.08
4	W	+	+	+	+	−	+	20	1.5	1.5
5	W	+	+	−	−	−	−	15	1.2	0.4
6	B	+	+	+	−	−	+	16	0.8	0.08
7	B	+	+	−	+	−	−	19	1.0	0.08
8	W	+	+	−	+	−	−	15	0.9	0.4
9	W	+	+	+	−	+	−	9	1.2	0.08
10	W	+	+	+	−	−	−	22	1.5	0.16

Patient	Vesicoureteral Reflux		Biopsy: Dysplasia Hypoplasia	Undescended Testicle		Bladder Wall Defect	Type 4 RTA	Hematuria	Proteinuria	ESRD Age (Years)	Years of Follow-Up
	L	R		L	R						
1	+	+	+	+	−	+	+	+	+++	15	20
2	+	−	NA	−	−	−	+	−	++	−	20
3	+	+	NA	−	−	−	+	−	++	7	17
4	+	+	NA	−	+	+	++	+	+	15	15
5	+	+	NA	−	−	−	−	−	+++	9	13
6	+	−	+	−	−	−	+	+	−	11	11
7	−	−	+	−	−	−	+	+	+	11	11
8	+	−	NA	−	−	−	−	−	Trace	−	4
9	+	+	+	−	−	+	+	+	+	3	3
10	−	−	NA	−	−	−	−	−	+	−	1

W indicates white; B, black; UTI, urinary tract infection; HBP, high blood pressure; BUN, blood urea nitrogen; Cr, creatinine; Bx, renal biopsy; NA, not applicable.

TABLE 2. Median Time to Serum Cr of 1.5, 2.5, 5.0, and 7.5 mg/dL

Cr (mg/dL)	Median Time to Cr (Years)	1/Cr	In (1/Cr)
1.5	1.20	0.666667	−0.40547
2.5	3.95	0.4	−0.91629
5.0	7.95	0.2	−1.60944
7.5	9.85	0.133333	−2.0149

Cr indicates creatinine.

hypertension (10%), palpable kidney/bladder or mass (20%), elevated blood urea nitrogen (100%), and elevated plasma creatinine (100%).

In all cases, posterior urethral valves were confirmed by postnatal voiding cystourethrograms and/or cystoscopy. Surgery was performed on 8 patients in the neonatal period and 2 at 1 to 1.5 years old, including primary valve ablation in 9, and vesicostomy in 4 (Table 1). In association with the valvular obstruction, we found renal dysplasia/hypoplasia (40%), undescended testicle (20%), bladder trabeculation and bladder cyst (30%), type 4 renal tubular acidosis (50%), hematuria (80%), and proteinuria (80%). Vesicoureteral reflux was documented in 8 patients: unilateral in 3 and bilateral in 5. Patients underwent reimplantation, resection of upper pole hypoplasia and/or stoma revisions. Over a follow-up of 11.5 ± 2.1 (mean ± standard error of the mean) years (Table 1), ESRD developed in 7 patients at 11.1 ± 2.0 years, all received maintenance dialysis and 4 subsequently received kidney transplantations. It is noteworthy that patients 3, 6, 7, and 9, all operated on at the youngest ages of the 10 patients in our series, are among those who went on to develop end-stage disease.

Analysis of the rising serum creatinine as an index of the rate of progression versus time in years (Fig 1) shows that once serum creatinine exceeded 5 mg/dL, the progression to ESRD was rapid, an average of $\Delta Cr/\Delta t = 1.32$. There was a slower rate of progression before this degree of renal compromise was reached, as shown by the data on time elapsed between creatinine of 1.5 to 2.5 mg/dL ($\Delta Cr/\Delta t = 0.57$) and from 2.5 to 5 mg/dL ($\Delta Cr/\Delta t = 0.63$). When the data were plotted on a log scale as the reciprocal of serum creatinine concentrations against time (Fig 2), there was a linear correlation ($r = 0.999$).

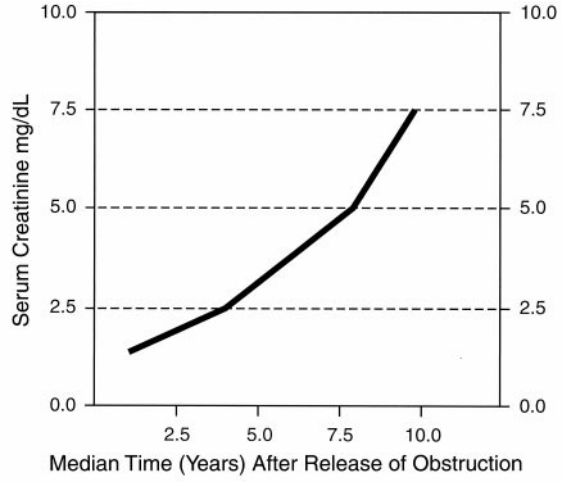

Fig 1. Serum creatinine elevation versus median time, in years, from nadir serum creatinine after relief of posterior urethral valve to serum creatinine of 2.5, 5.0, 7.5, and 10.0 mg/dL. Cr indicates serum creatinine in mg/dL.

DISCUSSION

Despite the compelling need to know the clinical prognosis of obstructive nephropathy, comparisons between previous studies are difficult because they differ greatly and frequently include a wide variety of upper and lower tract obstructions, different degrees of hydronephrosis/hydroureters and reflux, as well as nonobstructive (neurogenic) hydroureteronephrosis. In contrast, the present report is restricted only to our 21-year experience with posterior urethral valve obstruction. We have also reviewed our data in the light of other published series in English since the 1970s that were confined to study of posterior urethral valvular obstruction (Table 3). In addition, we have contrasted our experience with that reported in selected other series of obstructive uropathy, including but not exclusive to posterior urethral valves (Table 4).

The patient referral pattern to pediatric nephrology to this regional center was detailed elsewhere.[6] Over a 18.75-year period, we cared for 127 children with vesicoureteral reflux, hydronephrosis, and obstructive uropathy.[6,7] Posterior urethral valve is encountered in 1 of 10 000 to 25 000 births, making this one of the most common causes of congenital urologic malformations.[8–10] Since the 1970s, the widespread use of prenatal ultrasonographic screening has changed the pattern of referrals. Over the past 2 decades, the diagnosis has been usually made prenatally and surgical corrections performed earlier, which was the approach used in our patients (Table 1).

It is known that the rat kidney continues to develop more glomeruli and tubules for an additional month after birth, whereas human kidneys contain a complete nephron complement at birth. Thus, the more severe renal injury in neonatal rats secondary to unilateral obstructive uropathy[11] may be related to this developmental difference between the species. The question of whether the human neonatal kidney

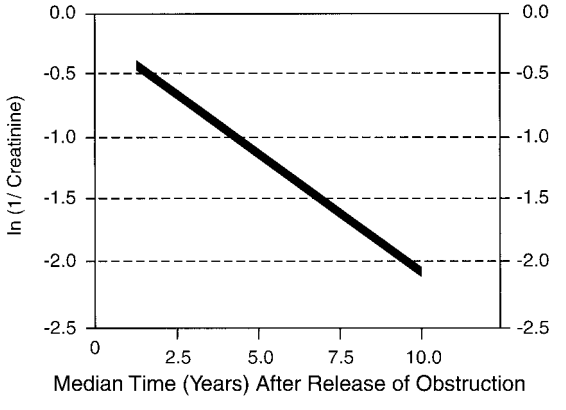

Fig 2. Natural logarithm of the inverse of serum creatinine, ln (1/Cr) versus median time in years, from nadir serum creatinine after relief of posterior urethral valve to serum creatinine of 2.5, 5.0, and 7.5 mg/dL. Cr indicates serum creatinine in mg/dL.

TABLE 3. Progression Rates for Patients With Posterior Urethral Valves to ESRD

Study Period	Year of Publication	First Author	Country	*n*	Diagnosis <1 Year of Age	Mean Serum Cr Preop (mg/dL)	% ESRD	Years From Diagnosis to ESRD	Follow-Up	Conclusions
1951–1970	1973	Williams[17]	United Kingdom	172	50%	NA	28%	NA	5.5 y	Mortality confined to uremia first y of life
1957–1978	1980	Krueger[18]	Canada	74	49%	1.95 ± 0.55	NA	NA	7.4 y	Initial diversion better than primary valvectomy
1970–1980	1983	Atwell[19]	United Kingdom	108	56%	NA	56%	NA	2.2 ± 0.6 y	High mortality with dysplasia
1972–1984	1985	Scott[20]	United Kingdom	46	65%	NA	28%	NA	0–12 y	Bilateral vesicoureteral reflux, poor prognosis
1971–1983	1985	Warshaw[21]	United States	22	100%	3.1	5%	NA	5.8 y	Nadir Cr <0.8 in first y, good prognosis
1966–1982	1986	Tejani[22]	United States	25	72%*	NA	44%	NA	9 y	Bilateral vesicoureteral reflux, poor prognosis; diverted group <1 y age ↑ Cr, poor prognosis
1966–1975	1988	Parkhouse[23]	United Kingdom	114	66%	NA	21%	NA	11–22 y	Upper tract diversion, poor prognosis. Early presentation <1 y of age, poor prognosis
1971–1985	1988	Rittenberg[24]	United States	119	NA	NA	30%	NA	1–14 y	Decompressing extravasation "pop off," good prognosis. Bladder drainage, 10% ↓ Cr, good prognosis
1975–1988	1990	Walker[25]	United States	32	100%	NA	37%	NA	NA	No difference between initial valvectomy vs vesicostomy
1976–1986	1990	Connor[26]	United States	50	100%	NA	24%	NA	7 y	At 1 y of age, Cr > 1 mg/dL, poor prognosis
1969–1979	1992	Merguerian[27]	Canada	102	10%	NA	12.7%	10 y	10 y	If GFR <30 mL/min/1.73 m², ESRD inevitable. Age of presentation, no prognostic value
1975–1990	1992	Reinberg[28]	United States	43	NA	NA	33%–63%	NA	NA	High or low diversion, no change
1975–1990	1992	Reinberg[29]	United States	24	100%	NA	33%†–64%‡	5.3 y	5.3 y	Nadir Cr >1.2 mg/dL, ESRD. Early diagnosis, did not improve prognosis
1987–1990	1993	Dinneen[30]	United Kingdom	42	100%	1.3–2.8	7%	2.5 y	2.5 y	Prenatal ultrasound 26 wk of gestation defect posterior ureteral valve
1965–1990	1993	Groenewegen[31]	The Netherlands	187	NA	NA	11%	9.8 y	NA	Renal transplant acceptable therapy
1982–1992	1994	Hutton[32]	United Kingdom	67	NA	NA	19%	3.9 y	NA	Respiratory distress, poor prognosis. Vesicoureteral reflux, not prognostic indicator
NA–1985	1996	Smith[33]	United States	100	56%	NA	13%	NA	11.5 y	High diversion, no advantage
1973–1990	1997	Denes[34]	United States	35	100%	5.6 ± 2.0	NA	NA	8.5 y	Nadir Cr after catheterization >0.8 mg/dL, poor prognosis. High diversion advocated
1969–1994	1998	Drozdz[35]	Germany	20	75%	NA	100%§	8.3 y	<21 y	Age <1 y, Cr >1.2 mg/dL, poor prognosis. Unilateral/bilateral VUR not prognostic indicator
1978–1999	Present report	Roth	United States	10	80%	3.4 ± 0.8	70%	11.1 y	1–20 y	Stable progression from serum creatinine 1.5–5 mg/dL, more rapid progression afterwards

NA indicates not available; Cr, creatinine. Represented 14% of all ESRD.
* Diagnosis <2 y of age.
† Neonatal diagnosis.
‡ Prenatal diagnosis.
§ Selected ESRD.

TABLE 4. Progression Rates for Patients With Obstructive Uropathy Including but Not Exclusive to Posterior Urethral Valves

Study Period	Year of Publication	First Author	Country	*n*	Diagnosis <1 Year of Age	Peak Cr Before First Surgery	% ESRD	Years From Diagnosis to ESRD	Follow-Up	Conclusions
1961–1971	1973	Habib[36]	France	57	NA	NA	37%	6.16 y	10.08 y	Reflux and posterior urethral valve, led to ESRD
NA	1975	Mayor[37]	Switzerland	24	50%	NA	NA	NA	1–12 y	Surgery <1 y of age, better prognosis. No correlation with urinary tract infections
1967–1978	1982	Warshaw[38]	United States	54*	41%	NA	100%	8.7 y	12.2 y	No gender difference in rate of progression. Surgery no effect on progression
1970–1982	1985	Mathieu[39]	France	125	65%	NA	18%	11.33 y	NA	Dietary protein and phosphate reduction is proposed to counter glomerular hyperfiltration and progression

NA indicates not applicable; Cr, creatinine.
* Selected from referral for ESRD care.

suffers more than does the adult kidney with ureteral obstruction remains unanswered. Given the continuing postnatal development, neonatal injury associated with unilateral ureteral obstruction in the rat would be expected to have more serious consequences compared with the human. Nevertheless, posterior urethral valve obstruction can be expected to cause injury to both kidneys.[12–16]

Indeed a majority of children with this condition progress to ESRD as demonstrated in our study (Table 1) and in other studies we reviewed (Table 3). An examination of Table 3 that summarizes the patient characteristics and outcome from 21 publications[17–35] to date on posterior urethral valves shows that in the earlier studies[17–24] from the decades of the 1970s and 1980s, there was a widely divergent proportion of patients who progressed to ESRD. There also seems to be little correlation between the length of follow-up and the incidence of ESRD. In the series of studies[25–35] published in the present decade, the tendency for the diagnosis of posterior urethral valve obstructive uropathy to be made before 1 year of age has moved toward 100%, as in our own cases (Table 1). Moreover, although diagnosis and intervention have been made much earlier, with sufficiently long follow-up the morbidity increases in a correlative manner.

In the recent publication by Drozdz et al[35] from Heidelberg, the mean rate of progression from diagnosis to ESRD was 8.3 years, which is close to the 11.1 ± 2.0 years in our study. The Heidelberg study[35] of 20 patients, all progressed to ESRD by 21 years of follow-up, with 50% of renal survival at 8.3 years. Thus, the data of Drozdz et al[35] and Reinberg et al[29] contrast with our data in valvular obstructive uropathy, and with the conclusions reached by Mayor et al[37] in 24 children with obstructive uropathy, including but not exclusive of posterior ureteral valve. However, Drozdz et al[35] showed that in patients diagnosed at the age of 0 to 9 months, ESRD occurred at a mean of 3.6 years, which is considerably lower than in the present study. In a retrospective study of 54 children with ESRD from various causes of obstructive uropathy, Warshaw et al[38] demonstrated no gender differences in the rate of progression and the rate was not affected by early versus later surgical correction.

In the last 3 decades, mortality of newborns from posterior ureteral valve[39–41] urinary obstruction has dropped remarkably from 20% to 45%[42] to 3% to 10%.[25,26,43] We have no neonatal mortality in our series (Table 1). Clearly, this significantly improved patient survival in the neonatal period, attributable to advances in prenatal and postnatal ultrasonography, surgical, and medical care, necessitated long-term outcome reevaluation. It will be important to further ascertain the rate of progression in humans after relief of obstruction and whether there is unrelenting progression, as suggested by animal studies,[4] as well as by our data shown in Figs 1 and 2.

With the exception of the 2 retrospective studies of Warshaw et al[38] and Drozdz et al,[35] whose patients were on dialysis/transplantation, the percentage of patients progressing from diagnosis to ESRD were

7% to 64% for those with posterior urethral valves (Table 3) and 18% to 52% in those with all types of obstructive uropathy including but not exclusive to posterior urethral valves (Table 4). In the latter series, the period from diagnosis to ESRD was 6.16 to 11.33 years (Table 4). In those with posterior urethral valves, the follow-up period varied from 2.5 years to 22 years (Table 3). The incidence of ESRD increases with the length of follow-up (Tables 1 and 3). Our data support these contentions of unrelenting progression in a sizable proportion of the patients followed for a sufficient period. In our series, 70% of corrected obstructive uropathy progressed to ESRD. Our data also show that the rate of progression seems to differ in different stages, slow at first until serum creatinine reaches 1.5 mg/dL, followed by a steady but slower rate from serum creatinine of 1.5 to 5.0 mg/dL (Fig 1). The rate of rise in serum creatinine was rapid after serum creatinine exceeded 5.0 mg/dL. It would seem that there is an urgent need to intervene with therapy in the earliest stage, to further extend the slow rate of progression before serum creatinine reaches 5 mg/dL.

Early intervention in obstructive uropathy has been attempted in utero.[44] These authors retrospectively reviewed the outcome of different fetal treatment modalities for a variety of congenital obstructive uropathies. The survival of prenatally versus postnatally treated infants with posterior urethral valves was reported to be 60% versus 93%, respectively. However, the critical factor was the lack of any alteration in the ultimate progression to ESRD in the prenatally treated group in comparison to the postnatally treated infants (31% vs 33%, respectively). In a subsequent publication,[45] the same group reported a long-term follow-up in a group of children who underwent vesicoamniotic shunt for fetal obstructive uropathy. The mean age of the children at follow-up was 54.3 months (range: 25–114). Of all 14 survivors, comprising several causes for the obstructive uropathy, 57% progressed over this time to ESRD, a figure approaching the 70% rate in our own patient population. Freedman et al[44,45] strongly emphasized how highly selective their patients were. They argued that by having selected the worst of the spectrum, the fetal group's outcome being equivalent to those treated postnatally, would suggest that in utero treatment provides some advantage.

Another conclusion that was reached by Freedman et al[45] was that interpretation of series that report obstructive uropathy outcomes without discrimination as to cause, severity, etc is problematic, a difficulty to which we have alluded in this report, as well. These authors called for greater standardization in diagnosis, treatment, and reporting as a first step toward better assessment of the efficacy of fetal intervention. We concur and suggest that the same issues require greater attention, irrespective of the time of intervention. The basis for a standardized therapeutic approach to various types of obstructive uropathy has been reviewed recently by Chevalier and Klahr.[46]

Thus, we have seen that the significant reduction in neonatal mortality from obstructive uropathy by virtue of early diagnosis by prenatal ultrasonography and well coordinated urologic and pediatric interventions has not averted the end-stage disease seen in earlier decades.[47] Any improvement in long-term survival of these patients will depend on preservation of renal function by ameliorating the consequences of hyperfiltration, infection, oxidative stress, and injury from other factors that may yet be determined.

CONCLUSION

Our data suggest that there is a segment of patients with posterior urethral valves that continues to have progressive renal deterioration despite prompt relief and that there is rapid progression to ESRD once serum creatinine exceeds 5.0 mg/dL. If there is any benefit of therapeutic intervention to slow the rate of progression, it needs to be applied before this level of serum creatinine.

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