Pediatr Nephrol (1992) 6: 412–416

Pediatric Nephrology

Original article

Prognosis of patients with unilateral renal agenesis

Luis R. Argueso[1], Michael L. Ritchey[1], Emmett T. Boyle, Jr.[2], Dawn S. Milliner[3], Erik J. Bergstralh[4], and Stephen A. Kramer[1]

[1] Department of Urology, [3] Division of Nephrology and Internal Medicine and Section of General Pediatrics and Pediatric Nephrology, and [4] Section of Biostatistics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA
[2] Section of Urology, Mayo Clinic Scottsdale, Scottsdale, Arizona, USA

Received August 1, 1991; received in revised form December 27, 1991; accepted March 6, 1992

Abstract. The clinical course was reviewed in 157 patients with unilateral renal agenesis and a normal contralateral kidney for the purpose of establishing a prognosis. There were 85 males (54%) and 72 females (46%). The mean age at diagnosis of unilateral renal agenesis was 37 years. The mean years at risk was 56. Proteinuria (>150 mg/24 h) was found in 19% of the 37 patients tested (P <0.001), hypertension developed in 47% of the 47 patients tested (P = 0.010), and renal function (adjusted for age and sex) was decreased in 13% of the 32 patients tested (P = 0.001). An increased filtration fraction was found in 7 (54%) of 13 patients evaluated. At the completion of this study, 114 patients (73%) were alive, and the survival rate was similar to that of age-, sex-matched United States life tables. Forty-three patients (27%) died; 6 deaths (4%) were caused by renal failure. Our review indicates that patients with unilateral renal agenesis and a normal solitary kidney are at increased risk of proteinuria, hypertension, and renal insufficiency. Therefore, it is essential to have prolonged and careful follow-up and to employ strategies that maximize renal preservation.

Key words: Hyperfiltration – Hypertension – Proteinuria – Renal insufficiency – Unilateral renal agenesis

Introduction

Urologists and nephrologists have routinely reassured patients that a single kidney is sufficient to meet the metabolic demands of the body without the development of proteinuria, hypertension, or renal insufficiency. The loss of functioning renal mass or the congenital absence of a kidney leads to hypertrophy of the remaining nephrons and, initially, renal function is well maintained. Hyperfiltration results in a decrease in both afferent and efferent arteriolar resistance. Because the reduction in resistance is greater in the afferent arteriole than in the efferent arteriole, the net result is an increase in the mean glomerular capillary pressure, which leads to an increase in the single nephron filtration rate [1]. It is generally believed that these functional changes in the remnant nephrons are beneficial, but experimental evidence suggests that the hemodynamic changes may in fact be maladaptive, leading to progressive destruction of the remaining glomeruli [2].

Sporadic clinical reports have documented the development of proteinuria and focal glomerulosclerosis in patients with unilateral renal agenesis (URA) and in patients who have undergone unilateral nephrectomy [3–8]. There are few studies, however, of renal function in these patients after years of follow-up [9, 10]. Most reports have focused on the outcome of adult patients who were renal donors for transplantation [2]. Patients with URA, or those who undergo nephrectomy in childhood, have a long interval in which their solitary kidney is exposed to hyperfiltration and its sequelae. We showed that the reduction of renal mass by nephrectomy during childhood is associated with an increased incidence of proteinuria and renal insufficiency [11].

To establish the incidence of proteinuria, hypertension, and renal insufficiency in patients with URA, we reviewed the clinical course of patients who were followed for more than 15 years from diagnosis.

Patients and methods

The clinical course was reviewed in 157 patients who were diagnosed with URA at the Mayo Clinic between 1960 and 1975. Radiographs were carefully reviewed and patients with vesicoureteral reflux, parenchymal scars, or any degree of hydronephrosis were excluded. All solitary kidneys showed radiological evidence of compensatory hypertrophy. Patients were excluded if they had proteinuria of 30 g/dl or greater or elevation of serum creatinine at the time of diagnosis, or if there was an associated anomaly, such as spina bifida, that could lead to renal deterioration. Forty-three patients (27%) had died, 6 from renal failure.

Correspondence to: S. A. Kramer, Department of Urology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Table 1. Medical profile of patients with unilateral renal agenesis (URA): a comparison of those with and those without follow-up laboratory data

Variable	Patients		P*
	No follow-up laboratory data (n = 119)	Follow-up laboratory data (n = 38)	
Sex (% male)	57	45	NS**
Age at diagnosis (median years)	39	34	NS
Event leading to diagnosis			
General medical examination (%)	47	70	0.012
Renal symptoms (%)	53[a]	30	
Died, % (no.)	36 (43)[b]	0	NA
Questionnaire			
Not completed, % (no.)	16 (19)	0	NA
Completed, % (no.)	48 (57)	100 (38)	NA
Response			
Diabetes (%)	5	6	NS
Hypertension (%)	18	41	0.014
Urinary tract infection (%)	25	25	NS
Kidney stones (%)	5	6	NS
Blood in urine (%)	5	11	NS
Protein in urine (%)	7	0	NS
Loss of kidney function (%)	7	3	NS
Other medical problems (%)	27	56	0.006
Removal of remaining kidney (%)	2	3	NS
Age at questionnaire (median years)[c]	49	55	NS

* Probability for a null hypothesis that postulates a similar distribution for both groups of patients; ** NS, $P > 0.10$

NA, Not applicable

[a] Of 6 patients who died of renal failure, 4 had renal symptoms at the time of diagnosis

[b] Value includes 6 patients who died of renal failure

[c] Same as years at risk

Nineteen patients (12%) chose not to participate in the study. Ninety-five patients (61%) responded to a detailed medical questionnaire. Measurements of 24-h creatinine clearance, 24-h urinary protein excretion, and blood pressure were obtained for 38 of the 114 surviving patients (33%). The adequacy of urine collection was assessed by total creatinine excretion adjusted for body weight [12]. Thirteen patients underwent study in our renal function laboratory. Glomerular filtration rate (GFR) was measured by inulin clearance, effective renal plasma flow was assessed by para-aminohippuric acid (PAH) clearance, and the filtration fraction was calculated.

The statistical comparison between groups was made using the chi-squared or rank sum test as appropriate. A one-sample chi-squared test was used to compare the percentage of patients with proteinuria, renal insufficiency, or hypertension with the expected percentage based on published reference limits [12, 13]. Survival from the day of URA diagnosis to death was estimated using the Kaplan-Meier method [14]. Expected survival was estimated using United States life tables for patients of matched sex, age, and year of birth.

There were 85 male patients (54%) and 72 (46%) female. The mean age at diagnosis of renal agenesis was 37 years (range 1–78 years). Females were diagnosed at an earlier mean age than males (32.9 vs 41.0 years, $P = 0.015$). The median follow-up after diagnosis was 19.1 years. The mean years at risk was 57. The left kidney was absent in 54% of the patients and the right kidney was absent in 46%. The diagnosis of URA was based on radiographic evaluation, including excretory urography, renal ultrasonography, computed tomography, or radioisotopic renal scans. URA was detected incidentally in 52% of patients during a general medical examination, and in 48% during evaluation of various urological complaints, such as nonfebrile urinary tract infections, microscopic hematuria, or flank pain.

Results

The medical history profile was similar in the group with follow-up laboratory data (n = 38) and the group without laboratory data (n = 119) (Table 1). Urological symptoms led to the diagnosis of URA more frequently among patients without laboratory data than in those with laboratory data. Hypertension and "other medical problems" were reported more frequently among those with laboratory data. Urinary tract infections were reported by 25% of the patients who responded to the questionnaire, hematuria was reported in 8%, diabetes mellitus in 5%, and renal calculi in 5%.

Proteinuria

Measurements of 24-h urinary protein excretion were performed in 37 patients. Proteinuria was defined as excretion of more than 150 mg/24 h. Proteinuria was found in 19% of these patients (n = 7) compared with the 2.5% expected ($P < 0.001$). Protein excretion in these 7 patients ranged from 161 to 1, 666 mg/24 h, with a mean protein excretion of 590 mg/24 h and a median of 185 mg/24 h. Three patients excreted more than 300 mg protein in 24 h.

For these 7 patients with proteinuria, the mean age at diagnosis of URA was 36 years (range 13–50 years), and the mean years at risk was 59 years (range 41–84 years). Of the 7 patients, 6 were male. Diabetes mellitus was present in only 1 patient with proteinuria. The mean age at diagnosis for the remaining 30 patients without proteinuria was 33 years, and the mean years at risk was 56 years (range 30–87 years).

Hypertension

Patients were considered to be hypertensive if systolic blood pressure was 160 mmHg or more, if diastolic blood pressure was 95 mmHg or more, or if the patient was receiving antihypertensive therapy [13]. Blood pressure measurements were available for 47 patients: 22 of these patients (47%) were hypertensive. When compared with age- and sex-specific reference limits, the incidence of hypertension (47%) was significantly higher than expected (28%) ($P = 0.010$).

Of the 22 patients with hypertension, 12 were female. The mean age at diagnosis of URA in these 22 patients was 40 years (range 15–57 years), and the mean years at risk was 63 years (range 38–83 years). None of the hypertensive patients had a history of diabetes mellitus.

Renal insufficiency

Creatinine clearance was measured in 32 patients. Renal insufficiency was defined according to age and sex from

Table 2. Serum creatinine and creatinine clearance in 32 patients

Sex	Age at assessment (years at risk), years	Serum creatinine (mg/dl)	Creatinine clearance (ml/min per 1.73 m²)	Renal insufficiency[a]
F	67	1.4	41	Yes
M	83	1.5	51	Yes
M	63	1.3	45	Yes
F	75	2.0	32	Yes
M	87	1.3	65	No
M	84	0.8	70	No
M	76	1.6	54	No
F	42	0.9	94	No
F	40	0.9	83	No
M	48	1.3	92	No
M	62	1.2	81	No
F	42	0.9	94	No
M	64	1.2	96	No
M	71	1.3	67	No
F	60	0.8	71	No
M	59	0.8	142	No
F	30	0.9	99	No
M	61	1.0	71	No
M	40	1.2	107	No
F	38	0.6	109	No
M	70	1.8	62	No
F	43	1.1	83	No
F	57	1.0	91	No
F	75	1.2	60	No
F	41	0.9	94	No
F	38	0.8	106	No
F	55	0.9	94	No
F	40	0.8	99	No
F	73	1.1	59	No
M	48	0.9	91	No
F	53	1.0	77	No
M	64	1.1	140	No

[a] The criterion for renal insufficiency was a value below the published age- and sex-specific lower limits for creatinine clearance

Table 3. Relationship between proteinuria, hypertension, and renal insufficiency in 27 patients with URA with at least one abnormality

Sex	Age at assessment (years)	Proteinuria[a] (mg/24 h)	Hypertension[b]	Renal insufficiency[c] (ml/min per 1.73 m²)
F	42	+317	–	–
M	40	+169	–	–
M	48	+161	–	–
M	61	+1, 666	–	–
M	64	+184	+	–
M	70	+1, 449	+	–
M	83	+185	+	+51
F	83	NE	+	NE
F	38	NE	+	NE
F	39	–	+	NE
F	42	–	+	–
F	53	–	+	–
F	57	–	+	–
F	59	NE	+	NE
F	60	–	+	–
F	68	NE	+	NE
F	73	–	+	–
F	75	–	+	–
M	71	–	+	NE
M	47	–	+	NE
M	59	–	+	–
M	64	–	+	–
M	67	NE	+	NE
F	67	–	+	+41
F	75	–	+	+32
M	76	–	+	–
M	63	–	–	+45
	Total +	7	22	4

+, Present; –, not present; NE, not evaluated

[a] Defined as excretion of >150 mg/24 h

[b] Patients were considered hypertensive if their systolic blood pressure was ⩾160 mmHg, if their diastolic blood pressure was ⩾95 mmHg, or if they were receiving medical treatment for hypertension

[c] Defined as having a creatinine clearance below published age- and sex-specific lower limits

previously published tables [12]. Individuals with a percentile rank less than 2.5% were considered to have renal insufficiency.

Renal insufficiency was found in 4 (13%) patients ($P = 0.049$). The mean creatinine clearance in patients with renal insufficiency was 42 ml/min per 1.73 m² (range 32–51 ml/min per 1.73 m²) (Table 2).

Of the 4 patients with renal insufficiency, 2 were male and 2 were female. The median age at diagnosis for these 4 patients was 51 years (range 48–58 years), and the mean years at risk was 76 years (range 68–84 years). None of the patients had diabetes mellitus. Table 3 shows the relationship between proteinuria, renal insufficiency, and hypertension. Table 4 compares the mean age at assessment, mean serum creatinine value, mean creatinine clearance, and mean years at risk for the patients who had renal insufficiency and the patients who did not have renal insufficiency.

Of the 13 patients who were studied with inulin and PAH clearances, 4 (31%) had a low GFR, 6 (46%) had a low effective renal plasma flow, and 7 (54%) had an increased filtration fraction (Table 5).

Table 4. Serum creatinine and creatinine clearance in patients with and without renal insufficiency

	Renal insufficiency ($n = 4$)	No renal insufficiency ($n = 28$)
Mean age at assessment (years)	72	56
Mean serum creatinine (mg/dl)	1.55	1.05
Mean creatinine clearance (ml/min per 1.73 m²)	42	88
Mean years at risk	72	56

Survival

At the time of this report, 114 patients (73%) were alive. Forty-three patients (27%) had died; 6 deaths were caused by renal failure. In our study population, survival from the day of URA diagnosis was similar to expected survival adjusted for age, sex, and year of birth (Fig. 1).

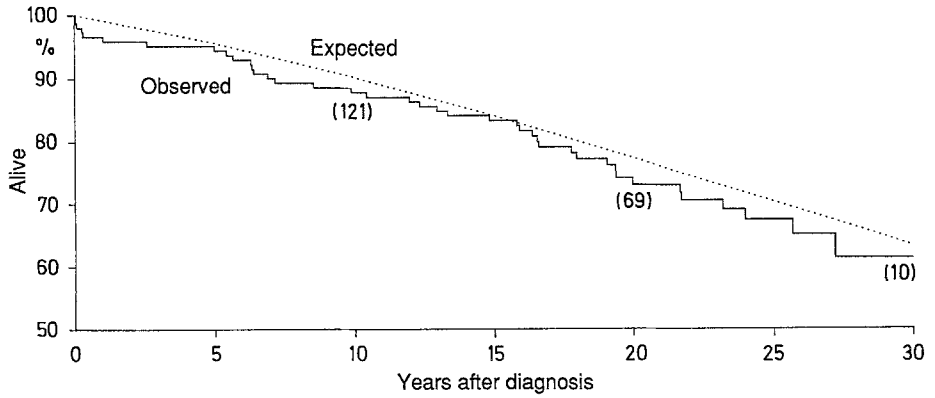

Fig. 1. Observed (———) and expected (...) survival for 157 patients with unilateral renal agenesis. Observed survival was similar to that based on United States life tables for patients of similar age, sex, and year of birth (expected). The number of patients at risk at 10, 20, and 30 years is given in parentheses. Survival was estimated by the Kaplan-Meier method

Table 5. Results from inulin and para-aminohippuric acid (PAH) clearance studies in 13 patients

Sex	Age (years)	GFR[a]	PAH[b]	Filtration fraction
M	87	64	247[c]	26[d]
F	67	36[c]	139[c]	26[d]
M	76	55[c]	231[c]	24[d]
F	42	80[c]	322[c]	25[d]
F	40	87	458	19
M	48	87	371	24[d]
M	62	85	379	22
F	30	99	526	19
F	57	76	336[c]	23[d]
F	39	84	435	19
F	38	115	527	22
F	40	76[c]	415	18
F	53	77	308[c]	25[d]

GFR, Glomerular filtration rate
[a] Glomerular filtration rate (ml/min per 1.73 m^2) measured by inulin clearance
[b] Effective renal plasma flow (ml/min per 1.73 m^2) measured by PAH clearance
[c] Lower than expected
[d] Higher than expected

Discussion

Children with URA are disadvantaged because they have decreased total renal mass from birth. Other congenital anomalies of the urinary tract are present in 20%–30% [15, 16]. These patients are usually evaluated with abdominal ultrasonography, which often leads to the diagnosis of URA or other defects. There are few reports of long-term outcome in patients with URA. Dees [17] evaluated 33 patients with congenital solitary kidney and found that disease other than hypertrophy developed in two-thirds. Of these patients, 8 had hydronephrosis due to obstruction other than a stone, 6 had renal stones, and 5 had chronic pyelonephritis. However, the length of follow-up was not reported. Emmanuel et al. [18] reviewed 74 cases of congenital solitary kidney and found vesicoureteral reflux in 11 patients, duplication anomalies in 3, and outlet obstruction in 2. Eleven patients had imperforate anus, and 2 patients had spina bifida. Patients were followed from 2 to 10 years. Hydronephrosis was found in 21 patients, 19 of whom needed corrective surgery. Six patients had renal stones and 8 patients had renal failure.

Ashley and Mostofi [19] examined 232 autopsy cases of URA. Renal disease was the cause of death in 36 patients (16%). This included chronic pyelonephritis in 20 patients, glomerulonephritis in 11, and nephrosclerosis in 5. More than half of these patients were older than 40 years at death. A significant proportion of these patients had other abnormalities of the remaining solitary kidney, including ectopic kidney, hydronephrosis, and ectopic ureter.

Although these studies suggest a poor prognosis for patients with URA, they may be biased by the fact that these are hospital-based series that select for patients who present with renal disease. These studies also do not specifically address the risk of renal deterioration in a solitary kidney that is otherwise normal at birth. Wikstad et al. [10] reported on the renal function of 15 patients with a diagnosis of URA and 21 patients who had undergone unilateral nephrectomy in childhood. They did not separate patients with URA from those who had undergone nephrectomy. All patients had a normal solitary kidney by radiographic evaluation. These patients lived for 7–40 years with a solitary kidney. Wikstad et al. [10] found that GFR slowly declined with age when compared with the GFR of age-matched patients with two kidneys and no renal disease. Longer follow-up (>26 years) revealed that 47 patients also had significant microalbuminuria that had increased progressively.

More than 20 cases of segmental and focal glomerular sclerosis have been reported in patients with URA [3–8]. Our patients were not subjected to renal biopsies and, therefore, we cannot document the presence or absence of glomerulosclerosis. However, the filtration fraction was elevated in 7 (54%) of the 13 patients evaluated. This is an important finding because it may explain the pathway to glomerulosclerosis. A reduction in total renal mass induces hypertrophy of the remnant kidney tissue with an increase in renal plasma flow and GFR per nephron. The increases in single nephron GFR, renal blood flow, and particularly the increased capillary pressures ultimately may lead to additional glomerular injury, proteinuria, and glomerulosclerosis.

Our study showed that patients with URA and a normal solitary kidney are at increased risk of proteinuria, hypertension, and renal insufficiency. Proteinuria and hypertension did not correlate with age, sex, age at diagnosis, or years at risk. However, there was a positive correlation between the likelihood of developing renal insufficiency

and years at risk. Patients with renal insufficiency had a mean of 72 years at risk compared with 56 years at risk for all patients. It is noteworthy that in addition to the 13% incidence of renal insufficiency among survivors, 4% of the patients had died of renal failure. Thus, our estimated rate of renal insufficiency (13%) was probably low.

Survival of our patient population from the date of URA diagnosis was similar to expected survival adjusted for age, sex, and year of birth (Fig. 1). Our study is limited by the fact that only 38 (33%) patients had follow-up laboratory data. However, a comparison of the group with laboratory data and the group without laboratory data reveals few differences (Table 1). Another possible limitation of the study is that other factors may be affecting the solitary kidney, such as incipient ureteropelvic junction obstruction, intermittent reflux, or previous infections. A great effort was made to exclude any kidney with reflux, any degree of hydronephrosis, or parenchymal scars. Our cases were obtained from a computerized data base of patients treated at a tertiary medical center, and about 50% were diagnosed because of renal symptoms. It is possible that the prognosis of our study group is worse than what one would see if an unbiased cohort was observed from the date of birth. With the increased use of in utero ultrasonography, such cohort studies should be possible in the future.

Prolonged and careful follow-up should be part of the management of patients with URA, including those with an apparently normal solitary kidney. Follow-up examination should include an annual measurement of blood pressure and urinalysis. Periodic measurements of urinary protein excretion and serum creatinine concentration are also indicated. Excision of renal mass should be avoided if at all possible. It is uncertain if early restriction of dietary protein or pharmacological methods of lowering glomerular capillary pressure will help prevent glomerular injury [20, 21].

In conclusion, patients with a solitary kidney due to URA have an increased incidence of proteinuria, hypertension, and renal insufficiency, even in the absence of structural anomalies of the kidney. Therefore, it is essential to have prolonged and careful follow-up and to employ strategies that maximize renal function.

References

1. Klahr S, Purkerson M, Harris K (1986) Mechanisms of progressive renal failure in experimental animals and their applicability to man. In: Brenner BM, Stein JH (eds) Contemporary issues in nephrology, vol 14. Churchill Livingstone, New York, pp 1182–1191
2. Anderson S, Meyer TW, Brenner BM (1985) The role of hemodynamic factors in the initiation and progression of renal disease. J Urol 133: 363–368
3. Kiprov DD, Colvin RB, McCluskey RT (1982) Focal and segmental glomerulosclerosis and proteinuria associated with unilateral renal agenesis. Lab Invest 46: 275–281
4. Weinstein T, Gafter U, Levi J, Zevin D, Ben-Bassat M (1985) Proteinuria and chronic renal failure associated with unilateral renal agenesis. Isr J Med Sci 21: 919–921
5. Rugiu C, Oldrizzi L, Lupo A, Valvo E, Loschiavo C, Tessitore N, Gammaro L, Ortalda V, Fabris A, Panzetta G, Maschio G (1986) Clinical features of patients with solitary kidneys. Nephron 43: 10–15
6. Thorner PS, Arbus GS, Celermajer DS, Baumal R (1984) Focal segmental glomerulosclerosis and progressive renal failure associated with a unilateral kidney. Pediatrics 73: 806–810
7. Gutierrez-Millet V, Nieto J, Praga M, Usera G, Martinez MA, Morales JM (1986) Focal glomerulosclerosis and proteinuria in patients with solitary kidneys. Arch Intern Med 146: 705–709
8. Bhathena DB, Julian BA, McMorrow RG, Baehler RW (1985) Focal sclerosis of hypertrophied glomeruli in solitary functioning kidneys of humans. Am J Kidney Dis 5: 226–232
9. Robitaille P, Lortie L, Mongeau J-G, Sinnassamy P (1985) Long-term follow-up of patients who underwent unilateral nephrectomy in childhood. Lancet I: 1297–1299
10. Wikstad I, Celsi G, Larsson L, Herin P, Aperia A (1988) Kidney function in adults born with unilateral renal agenesis or nephrectomized in childhood. Pediatr Nephrol 2: 177–182
11. Argueso LR, Ritchey ML, Boyle ET Jr, Milliner DS, Bergstralh EJ, Kramer SA (1992) Prognosis of children with solitary kidney after unilateral nephrectomy. J Urol (in press)
12. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW (1976) The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. J Gerontol 31: 155–163
13. Drizd T, Dannenberg AL, Engel A (1986) Blood pressure levels in persons 18–74 years of age in 1976–80, and trends in blood pressure from 1960 to 1980 in the United States. Vital Health Stat [11] 234: 1–68
14. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481
15. Doroshow LW, Abeshouse BS (1961) Congenital unilateral solitary kidney: report of 37 cases and a review of the literature. Urol Survey 11: 219–229
16. Longo VJ, Thompson GJ (1952) Congenital solitary kidney. J Urol 68: 63–68
17. Dees JE (1960) Prognosis of the solitary kidney. J Urol 83: 550–552
18. Emmanuel B, Nachman R, Aronson N, Weiss H (1974) Congenital solitary kidney: a review of 74 cases. Am J Dis Child 127: 17–19
19. Ashley DJB, Mostofi FK (1960) Renal agenesis and dysgenesis. J Urol 83: 211–230
20. Mitch WE (1984) The influence of the diet on the progression of renal insufficiency. Annu Rev Med 35: 249–264
21. Anderson S, Rennke H, Brenner BM (1986) Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. J Clin Invest 77: 1993–2000