Hypertension and Progression of Chronic Renal Insufficiency in Children: A Report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS)

MARK MITSNEFES,* PING-LEUNG HO,† and PAUL T. MCENERY*
**Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; and †EMMES Corporation, Potomac, Maryland.*

Abstract. Hypertension frequently complicates the course of chronic renal insufficiency (CRI) in children. This study sought to define the role of hypertension in progression of CRI in children by using the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) CRI database. The study cohort consisted of 3834 patients aged 2 to 17 yr with an estimated GFR (eGFR) ≤75 ml/min·1.73 m^2 enrolled onto NAPRTCS. The time to end point was defined as the time between registry enrollment and progression to renal substitution therapy or a 10 ml/min·1.73 m^2 drop in GFR from baseline, whichever was first. Forty-eight percent of the study patients had hypertension at baseline. There was a significant difference in reaching end points between hypertensive and normotensive children (58% *versus* 49%, respectively, $P < 0.001$). Significant difference in outcome between hypertensive and nonhypertensive patients was seen in children with eGFR 50 to 75 ml/min·1.73 m^2 ($P < 0.001$). Multivariate Cox regression modeling demonstrated that systolic hypertension was a significant independent predictor of progression of CRI ($P = 0.003$). Other significant predictors of CRI progression in this model included older age ($P = 0.0001$), African American ethnicity ($P = 0.03$), acquired cause of renal disease ($P = 0.0001$), and baseline eGFR <50 ml/min·1.73 m^2 ($P = 0.0001$). Hypertension is a highly significant and independent predictor for progression of CRI in children.

Studies in adults have confirmed that high BP is associated with a faster rate of decline in kidney function in patients with diabetic or nondiabetic nephropathies as well as in the general population. Recently, the Kidney Disease Outcome Quality Initiative, assembled by the National Kidney Foundation, reviewed the results of 26 studies of adults, which showed a significant relationship between hypertension and progression of chronic kidney disease (1). As in adults, hypertension is a frequent complication in children with chronic renal insufficiency (CRI). The data from the 1996 annual report of North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) (2) indicated that 34% of children with CRI were receiving antihypertensive treatment, with the percentage especially high in patients with polycystic kidney disease (83%) and glomerulopathies (71%). In contrast to numerous adult studies, there is a paucity of information related to the effect of BP on progression of CRI in children. By using the large NAPRTCS CRI database, we undertook a study to determine the role of hypertension in progression of CRI in pediatric patients.

Materials and Methods

Data that had been collected since 1994 were obtained retrospectively from the CRI NAPRTCS database. This report includes all data received in the data coordinating center through December 2001. Data were collected at the time of the enrollment of a patient onto NAPRTCS and every 6 mo thereafter. The study cohort included 3834 patients between 2 and 17 yr of age who had at the time of enrollment an estimated GFR (eGFR) ≤75 ml/min·1.73 m^2 as calculated by the Schwartz formula (3). Data obtained at baseline included age, gender, race, primary renal diagnosis, systolic BP (SBP), diastolic BP (DBP), use of BP medications, weight, height, body mass index (BMI), and eGFR. Mild CRI was defined as eGFR 50 to 75 ml/min·1.73 m^2, moderate CRI as eGFR 25 to 49 ml/min·1.73 m^2, and severe renal failure as eGFR <25 ml/min·1.73 m^2. Hypertension was defined as either SBP or DBP ≥95th percentile for gender, age, and height (4) at baseline. The time to end point was defined as the time between registry enrollment and progression to renal substitution therapy or time to a 10-ml/min·1.73 m^2 drop from baseline eGFR, whichever happened first.

Contrast between hypertensive and normotensive patients was assessed by the log-rank test. Survival analysis first used the Kaplan-Meier method. A multivariate Cox regression model was then used to assess independent predictors for outcome. Relative risk was adjusted for potential variables including hypertension (yes *versus* no), eGFR (<50 ml/min·1.73 m^2 *versus* ≥50 ml/min·1.73 m^2), age (<5 yr *versus* ≥5 yr), race (white *versus* nonwhite), BMI (<95th percentile *versus* ≥ 95th percentile), and primary renal diagnosis (acquired *versus* structural).

Received March 12, 2003. Accepted July 15, 2003.
Correspondence to Dr. Mark Mitsnefes, Division of Nephrology and Hypertension, MLC: 7022, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229-3039. Phone: 513-636-4531; Fax: 513-636-7407; E-mail: Mark.Mitsnefes@cchmc.org
1046-6673/1410-2618
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000089565.04535.4B

Results

Among the cohort of 3834 children, the majority were boys (63.3%) and were white (62%); 18.3% were African American, and 14.3% were Hispanic. The primary kidney diagnosis included structural anomalies/familial diseases (60.5%), glomerulonephritis or focal segmental glomerulosclerosis (13.8%), systemic immunological disease (7.3%), and others (18.5%). At baseline, 33% had mild CRI, 41% had moderate CRI, and 26% had severe chronic renal failure. There were 341 children (8.9%) with BMI ≥95th percentile.

Systolic hypertension, diastolic hypertension, or both was present at baseline in 1847 patients (48%). Systolic hypertension only was present in 41%, diastolic hypertension only in 28%, and both systolic and diastolic hypertension in 34%. The characteristics of hypertensive and normotensive patients at baseline are listed in Tables 1 and 2. Hypertensive children were younger ($P < 0.001$) and had lower eGFR ($P < 0.01$). There were more African Americans ($P = 0.02$), obese patients ($P < 0.001$), and those with acquired kidney disease ($P < 0.001$) in the hypertensive group than in the group of children with normal BP. One-third of normotensive children and one-half of hypertensive children were receiving antihypertensive medications at baseline.

Kaplan-Meier analysis demonstrated that there was a significant difference between hypertensive and normotensive children in reaching end points (58% *versus* 49%, respectively, $P < 0.0001$, Figure 1). Separate analysis for systolic or diastolic BP showed that both systolic ($P < 0.0001$) and diastolic ($P < 0.0001$) hypertension were associated with more rapid progression. A significantly greater rate of progression to end points was seen in patients with eGFR 50 to 75 ml/min·1.73 m^2 at baseline if they were hypertensive ($P < 0.001$). The rate was not significantly different between normotensive and hypertensive patients with baseline eGFR <50 ml/min·1.73 m^2 (Figure 2).

Multivariate Cox regression modeling was performed to determine whether the detrimental effect of increased BP was independent of other known risk factors for progression of CRI. This analysis demonstrated that systolic hypertension was a significant independent predictor of progression of CRI ($P = 0.003$). Other significant predictors of more rapid CRI progression in this model included older age ($P = 0.0001$), African American ethnicity ($P = 0.03$), acquired cause of renal disease ($P = 0.0001$), and baseline eGFR <50 ml/min·1.73 m^2 ($P = 0.0001$) (Table 3). Diastolic hypertension did not remain in the final regression model as an independent risk factor for the progression of CRI.

Discussion

This retrospective analysis of pediatric patients with CRI from the NAPRTCS database demonstrated a high prevalence (48%) and a close correlation of hypertension with progression of renal failure. The results of this large study are in agreement with adult studies demonstrating that high BP is associated with accelerated deterioration of kidney function. We showed in children that these relationships appeared to be causal because hypertension predicted progression of CRI independently of other known risk factors such as baseline kidney function, age, race, and primary kidney diagnosis. In adults, hypertensive nephrosclerosis is the second most frequent cause of end-stage renal disease. Contrary to adult patients, in children with CRI, the elevated BP is considered to be simply a

Table 1. Demographic characteristics at baseline in normotensive and hypertensive children with chronic renal insufficiency

Variable	Normotensive ($n = 1987$)	Hypertensive ($n = 1874$)
Age, *n* (%)		
2 to 5[a]	383 (19.3)	457 (24.7)
6 to 12	876 (44.1)	770 (41.7)
12 to 17	728 (36.6)	620 (33.6)
Gender, *n* (%)		
male	1278 (64.3)	1147 (62.1)
female	709 (35.7)	700 (37.9)
Race, *n* (%)		
white	1257 (63.3)	1108 (60)
African American[a]	332 (16.7)	383 (20.7)
Hispanic	290 (14.6)	255 (13.8)
other	108 (5.4)	101 (5.5)
Diagnosis, *n* (%)		
dysplasia	324 (16.3)	246 (13.3)
congenital/familial	946 (47.6)	790 (42.8)
HUS/systemic immunologic	117 (5.9)	157 (8.5)
glomerulonephritis/focal segmental glomerulosclerosis[a]	223 (11.2)	323 (17.5)
other	377 (19)	331 (17.9)

[a] Significant difference ($P < 0.05$) between children with and without hypertension.

Table 2. Clinical characteristics at baseline in normotensive and hypertensive children with chronic renal insufficiency[a]

Variables	Normotensive (n = 1987)	Hypertensive (n = 1874)
Height SDS	−1.4 ± 0.04	−1.3 ± 0.03
Height percentiles	23.1 ± 0.63	23.0 ± 0.61
Weight SDS[b]	−0.8 ± 0.04	−0.5 ± 0.03
Weight percentiles	34.2 ± 0.75	40.4 ± 0.81
BMI,[b] (kg/m^2)	18.8 ± 0.12	19.7 ± 0.13
BMI SDS	−0.01 ± 0.04	0.3 ± 0.03
BMI <95th percentile, *n* (%)	1851 (93.2)	1633 (88.4)
BMI ≥95th percentile, *n* (%)[b]	136 (6.8)	214 (11.6)
Estimated GFR[b] (ml/min/1.73 m^2)	41.0 ± 0.4	39.2 ± 0.4
<25, *n* (%)	489 (24.6)	509 (27.6)
25 to 49, *n* (%)	806 (40.6)	778 (42.1)
50 to 75, *n* (%)	692 (34.8)	560 (30.3)
Blood pressure[b]		
systolic (mmHg)	106.8 ± 0.3	127.1 ± 0.4
diastolic (mmHg)	63.3 ± 0.2	77.6 ± 0.3
Antihypertensive medication[b] (%)		
yes	35.6	48.7
no	64.6	51.3

[a] Data are presented as mean ± SD, unless otherwise specified. BMI indicates body mass index.
[b] Significant difference ($P < 0.05$) between children with and without hypertension.

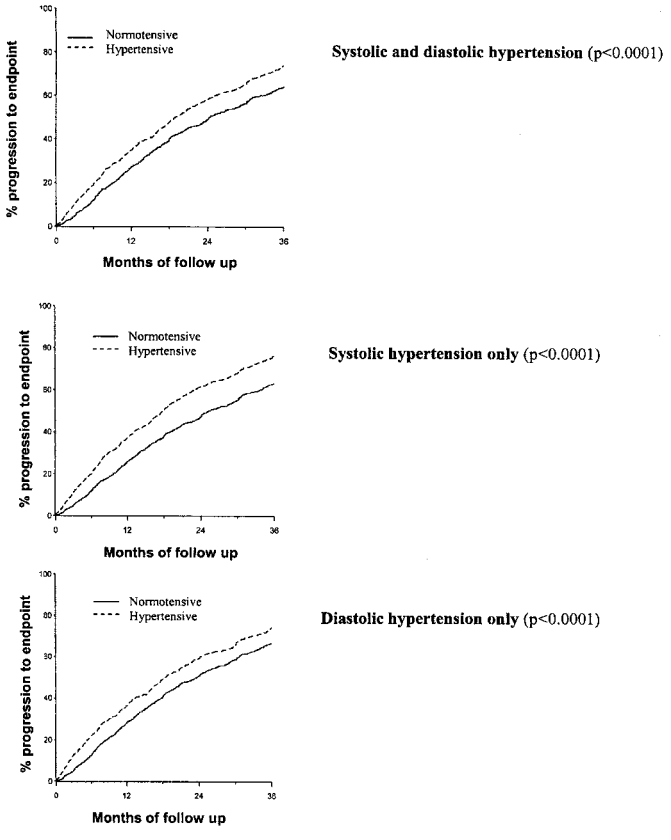

Figure 1. Survival analysis by baseline hypertensive status. (Top) systolic and diastolic hypertension; (middle) systolic hypertension only; (bottom) diastolic hypertension only. $P < 0.0001$.

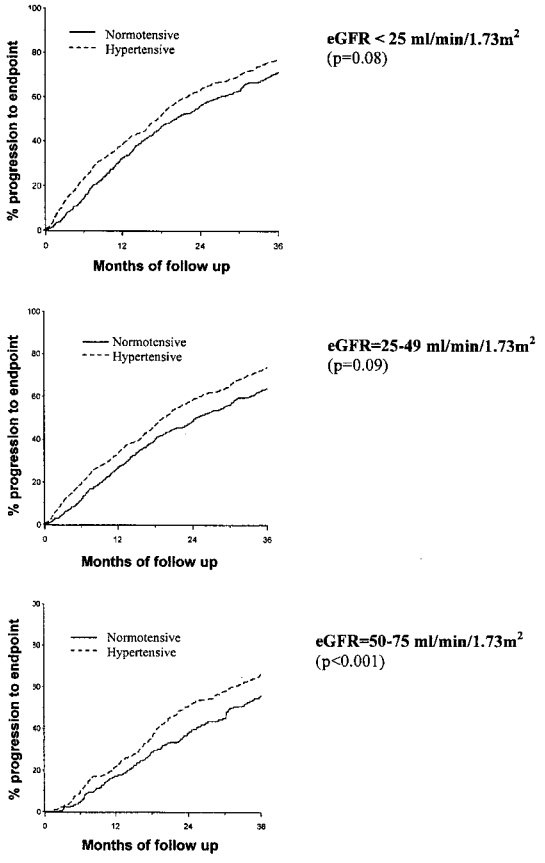

Figure 2. Survival analysis by baseline hypertensive status and estimated GFR (eGFR) < 25 ml/min/1.73m^2 ($P = 0.08$) (top); 25 to 49 ml/min/1.73m^2 ($P < 0.001$) (bottom).

Table 3. Multivariate Cox regression model of progression of chronic renal insufficiency

Variable	Relative Risk (95% CI)	*P* Value
Systolic hypertension (yes *versus* no)	1.20 (1.09 to 1.33)	0.003
Diastolic hypertension (yes *versus* no)	1.10 (0.99 to 1.22)	0.08
Ages 6 to 12 *versus* 2 to 5 (yr)	1.29 (1.15 to 1.46)	0.0001
Ages 13 to 17 *versus* 2 to 5 (yr)	1.91 (1.67 to 2.17)	0.0001
White *versus* nonwhite	0.90 (0.82 to 0.99)	0.03
Body mass index ≥95th percentile *versus* <95th percentile	1.16 (0.99 to 1.37)	0.07
Estimated GFR ≥50 *versus* <50 (ml/min/1.73 m^2)	0.55 (0.51 to 0.58)	0.0001
Structural *versus* acquired cause of chronic renal insufficiency	0.55 (0.47 to 0.66)	0.0001

marker of severity of the disease. The study presented here shows that hypertension is not only a marker, but also a significant risk factor for progressive renal dysfunction.

In the study presented here, SBP but not DBP remained as an independent predictor for the progression of renal failure in the final model of our multivariate analysis. These data are in agreement with the pediatric study by Wingen *et al.* (5), in which the authors prospectively evaluated the effect of a low-protein diet on the progression of chronic renal failure. They showed that SBP >120 mmHg and not DBP, and proteinuria were associated with high rates of decline of renal function. However, a SBP of 120 mmHg is an imprecise indicator of hypertension. It might represent significant hypertension in the young child or be normal in the adolescent. To adjust for the difference in size among subjects, the study presented here used SBP and DBP 95th percentiles for gender, age, and height for normal children to define hypertension in our study.

Analysis based on the level of renal function at baseline showed that in children with advanced renal failure (eGFR <50 ml/min·1.73 m^2), hypertensive patients deteriorated more rapidly than normotensive patients, but the difference was not statistically significant. One could argue that in those with severe disease, the disease would have progressed regardless of hypertension. Yet hypertension was strongly associated with progression of renal failure in children with eGFR >50 ml/min·1.73 m^2. This observation suggests that an elevated BP is especially harmful and evident in children with mild renal impairment.

From our retrospective study, we could not conclude which BP level is safe and what the target BP should be to prevent or slow hypertension injury to the kidney. In adults with CRI, current recommendations are based on the results of the large randomized trial on strict BP control from the Modification of Diet in Renal Disease Study (6). The BP goal for adult patients with CRI and proteinuria is 125/75 mmHg and without proteinuria 135/85 mmHg. However, recently published results from the African American Study of Kidney Disease and Hypertension argued that a low BP goal is not necessary (7). In this interventional study, adults with hypertensive renal disease were assigned to low or casual BP goals. Achieved average BP 128/78 mmHg (low BP goal) had no additional benefit of slowing progression of renal failure when compared with achieved average BP 141/85 mmHg (casual BP goal). The BP that will delay the progression of chronic renal failure is currently being examined in the European pediatric multicenter study. In this 3-yr trial, children with CRI treated with angiotensin-converting enzyme inhibitor (ramipril) are randomized to a target BP below 50th percentile or between 50th and 95th percentile on the basis of the 24-h ambulatory BP monitoring standards (8). The results of this trial will not be available until 2004.

In the study presented here, we decided not to use treatment with antihypertensive medication to define hypertension. The use of BP medications as a marker of hypertension has significant limitations. Specifically, it says nothing about the level of BP control, and it does not accurately identify those receiving medications but with good BP control. Other children might be hypertensive while receiving medication. Indeed, in this study, more than one half of children with elevated BP did not receive any antihypertensive treatment. In contrast, one third of normotensive children were taking BP medications. In addition, data concerning time of initiation, type, dosage, and numbers of antihypertensive medications are not currently collected by NAPRTCS. Other limitations of this retrospective study are our inability to fully control for all confounding variables related to the progression of CRI. Specifically, data for the level of proteinuria, duration of kidney disease, comorbid conditions, and the use of immunosuppressive medications were not available. Also, kidney function was estimated on the basis of serum level of creatinine, and the differences among laboratories in creatinine calibration might lead to error in estimation of GFR by as much as 20%, which is especially evident in patients with mild renal insufficiency (9). The variability in the methodology for BP measurement among participating centers could also affect the results of the study.

In summary, this large study of children with CRI has demonstrated a strong independent relationship between high BP and accelerated progression of renal failure. The study presented here demonstrates the potential value of large-scale prospective studies of the effect of BP on long-term outcome in pediatric patients with chronic kidney disease, especially in those with mild renal impairment.

Acknowledgments

The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) is a voluntary collaborative effort comprising more than 140 pediatric renal disease treatment centers in the United States,

Canada, Mexico, and Costa Rica. It is supported by major unrestricted grants from Novartis, Amgen, and Genentech. The results were presented in part at the 2002 ASN meeting, Philadelphia, PA.

References

1. NKF K/DOQI clinical practice for chronic kidney disease: Evaluation, classification, and stratification—Stratification of risk for progression of kidney disease and development of cardiovascular disease. *Am J Kidney Dis* 39[Suppl 1]: S170–S179, 2002
2. Fivush BA, Jabs K, Neu AM, Sullivan EK, Feld L, Kohaut E, Fine R: Chronic renal insufficiency in children and adolescents: The 1996 annual report of NAPRTCS. *Pediatr Nephrol* 12: 328–337, 1998
3. Schwartz GJ, Haycock GB, Edelman CM Jr, Spitzer A: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 58: 259–263, 1976
4. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. *Pediatrics* 98: 649–658, 1996
5. Wingen AM, Fabian-Bach, Schefer F, Mehls. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. *Lancet* 349: 1117–1123, 1997
6. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, King AJ, Klahr S, Massry SG, Seifter JL: Blood pressure control, proteinuria, and the progression of renal disease: The Modification of Diet in Renal Disease Study. *Ann Intern Med* 123: 754–762, 1995
7. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG; Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK Trial. *JAMA* 288: 2421–2431, 2002
8. Soergel M, Kirschstein M, Busch C, Danne T, Gellermann J, Holl R, Krull F, Reichert H, Reusz GS, Rascher W: Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: A multicenter trial including 1141 subjects. *J Pediatr* 130: 178–184, 1997
9. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, Levey AS: Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 39: 920–929, 2002