Family History of End-Stage Renal Disease among Incident Dialysis Patients

BARRY I. FREEDMAN,* J. MICHAEL SOUCIE,† and WILLIAM M. McCLELLAN‡
**Department of Internal Medicine/Nephrology, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina; †Department of Epidemiology, Emory University School of Public Health, Atlanta, Georgia; and ‡Departments of Internal Medicine and Public Health, Emory University School of Medicine, Atlanta, Georgia.*

Abstract. As part of a larger study of genetic risk factors for the occurrence of renal failure, the prevalence of a family history of end-stage renal disease (ESRD) in first- and second-degree relatives of all incident dialysis patients treated in Georgia, North Carolina, and South Carolina (ESRD Network 6) in 1994 was ascertained. Family histories were obtained from 4365 dialysis patients (83% of those eligible), and 856 (20%) reported having a family history of ESRD. Among race-sex groups, 14.1% of Caucasian men, 14.6% of Caucasian women, 22.9% of African-American men, and 23.9% of African-American women reported a first- or second-degree relative with ESRD ($P = 0.001$). The prevalence of relatives with ESRD varied by the reported etiology: 22.2% in diabetes mellitus; 18.9% in hypertension, 22.7% in glomerulonephritis; and 13.0% of other etiologies ($P = 0.001$). Patient characteristics independently associated with family history of ESRD included race, younger age, higher levels of education, and etiology of ESRD. In this report, it is concluded that a large proportion of incident ESRD cases have close relatives with ESRD in whom preventive actions might be directed. Genetic analyses in multiply affected families may identify the inherited factors contributing to progressive renal failure. (J Am Soc Nephrol 8: 1942–1945, 1997)

The incidence rate of end-stage renal disease (ESRD) is markedly higher in African-Americans compared with Caucasians in the United States (1). The elevated risk of ESRD in African-Americans is independent of differences in socioeconomic status and prevalence of hypertension and diabetes mellitus (2–4). Several studies (5–8) have demonstrated a consistent familial aggregation of ESRD in African-American, and, to a lesser extent, Caucasian families (9). However, no study has assessed the familial clustering of ESRD in a large cohort of new patients from a wide geographic area. The purpose of this study was to determine how often incident dialysis patients reported first- or second-degree relatives with ESRD and to identify risk factors associated with the familial clustering.

Materials and Methods

The study population comprised all patients who initiated Medicare-supported renal replacement therapy in ESRD Network 6 dialysis facilities (North Carolina, South Carolina, and Georgia) during 1994 (10). Eligible patients had ESRD attributed to diabetes mellitus, hypertension, primary or systemic diseases with glomerular involvement, or other etiologies by the treating nephrologist. We excluded from the analyses patients with ESRD attributed to adult polycystic kidney disease, Alport's syndrome, or urologic disease (surgical nephrectomy, reflux nephropathy, etc.).

A standardized data collection instrument was used to record the number of siblings and children of each incident dialysis patient, the names, vital status, and addresses of relatives with ESRD, and the name, address, and phone number of a relative without ESRD to serve as a family contact. Facility staff members, primarily social workers or nurses, collected this information during the patient's initial visit to a facility. Data were entered into a computer data base by network staff.

Statistical Analyses

The family history was considered positive if an incident ESRD patient (index case) reported having either a first-degree (parent, sibling, or child) or second-degree (grandparent, aunt, uncle, grandchild, or half sibling) relative with ESRD. The ratios of the proportion of patients with a positive family history (prevalence ratio) were used to estimate the crude relative risk for levels of demographic and clinical characteristics (11). Adjustment for the simultaneous influence of characteristics associated with risk for ESRD (age, race, sex, state of residence, and cause of ESRD) was performed using logistic regression analysis with family history of ESRD (yes or no) as the outcome variable (12). White men served as the index group for the race-gender analyses because they had the fewest relatives with ESRD. For the same reason, etiologies of ESRD other than hypertension, diabetes, and glomerular disease served as the index group for the cause of ESRD analyses. Residence in Georgia, a younger age at onset of ESRD (<45 yr), and fewer years of formal education (0 to 8 yr) were randomly selected as index criteria for their respective analyses.

Received February 17, 1997. Accepted May 5, 1997.
Correspondence to Dr. Barry I. Freedman, Bowman Gray School of Medicine, North Carolina Baptist Hospital, Medical Center Boulevard, Winston-Salem, NC 27157-1053.
1046-6673/08012-1942$03.00/0
Journal of the American Society of Nephrology

Results

A total of 5236 patients initiated renal replacement therapy for ESRD in Network 6 facilities during 1994 and were eligible for inclusion in the study. Family history data were collected for 4365 (83%) of these patients. After the exclusion of 76 patients who self-reported their race as other than African-American or Caucasian, 4289 patients remained in the study group.

The mean (SD) age was 58.4 (15.6) yr, and 79% were aged 45 or older (Table 1). African-American women comprised the largest race-sex group, and 62% of all patients were African-American. Forty percent of cases reportedly had ESRD associated with diabetes mellitus, 39% with hypertension, 10% with chronic glomerular diseases (primary or systemic disease combined), and 11% with other etiologies. Nearly half of patients had 8 yr of formal education or less.

A positive family history of ESRD was reported by 856 (20%) of the 4289 incident dialysis patients. Family members reported as having ESRD included parents of 258 (30%) patients, children of 54 (6%), siblings of 351 (41%), half-siblings of 20 (2%), uncles or aunts of 128 (15%), grandparents of 43 (5%), and grandchildren of two patients.

The prevalence of a positive family history varied according to the level of demographic and clinical characteristics of the case patients (Table 1). The prevalence decreased with age, was higher among African-Americans than Caucasians, and was higher among people with some high school compared to those with either less or more formal education. Compared to patients with other causes of ESRD, the prevalence of a positive family history was 50% higher for patients with ESRD from hypertension and nearly twice as high for patients with glomerulonephritis or diabetes as the cause of ESRD. No differences in the prevalence of a family history of ESRD were detected between the three states comprising ESRD Network 6. These associations between demographic and clinical characteristics and family history of ESRD persisted when the simultaneous influence of these factors was examined using a multivariate model (Table 2).

Discussion

This study reports on the familial clustering of ESRD in a large incident cohort of dialysis patients. Our findings strongly support earlier reports of familial aggregation of ESRD and are relevant for several reasons. First, the incidence rates of ESRD are highest in the Southeast region of the United States (10). If 20% of incident patients have additional family members at risk for ESRD, then our findings may help identify these individuals so that they may be targeted for interventions aimed at delaying or preventing renal failure. For example, a family history of nephropathy is a reliable predictor of whether diabetic individuals will develop future renal failure (7,13,14). Increased screening among at-risk family members and early institution of angiotensin-converting enzyme inhibitors at the

Table 1. Demographic and clinical characteristics and associations with family history of ESRD among 4289 incident dialysis patients, ESRD Network 6, 1994[a]

Factor	*n* (%)	Family History *n* (%)	Prevalence Ratio (95% CI)
Age level			
<45	906 (21)	220 (24.3)	
45 to 64	1688 (39)	362 (21.4)	0.9 (0.8to1.0)
65+	1695 (40)	274 (16.2)	0.7 (0.6to0.8)
Race-sex group			
Caucasian men	915 (21)	129 (14.1)	
Caucasian women	725 (17)	106 (14.6)	1.0 (0.8to1.3)
African-American men	1172 (27)	268 (22.9)	1.6 (1.3to2.0)
African-American women	1477 (35)	353 (23.9)	1.7 (1.4to2.0)
State of residence			
Georgia	1525 (36)	313 (20.5)	
North Carolina	1775 (41)	343 (19.3)	0.9 (0.8to1.1)
South Carolina	989 (23)	200 (20.2)	1.0 (0.9to1.3)
Education level			
0 to 8 yr	1989 (46)	354 (17.8)	
9 to 12 yr	1707 (40)	385 (22.6)	1.3 (1.1to1.4)
>12 yr	593 (14)	117 (19.7)	1.1 (0.9to1.3)
Cause of ESRD			
other	461 (11)	60 (13.0)	
hypertension	1658 (39)	313 (18.9)	1.5 (1.1to1.9)
glomerulonephritis	450 (10)	102 (22.7)	1.7 (1.3to2.3)
diabetes mellitus	1720 (40)	381 (22.2)	1.7 (1.3to2.2)

[a] ESRD, end-stage renal disease; CI, confidence interval.

Table 2. Independent associations between demographic and clinical characteristics and family history of ESRD among 4289 incident dialysis patients, ESRD Network 6, 1994[a]

Factor	Level	Odds Ratio (95% CI)
Age	45 to 64	0.8 (0.7to1.0)
	65+	0.7 (0.5to0.8)
Race-sex group	Caucasian women	1.1 (0.8to1.4)
	African-American men	1.8 (1.4to2.3)
	African-American women	1.9 (1.5to2.4)
Education (yr)	9 to 12	1.3 (1.1to1.5)
	>12	1.1 (0.9to1.5)
Cause of ESRD	Hypertension	1.5 (1.1to2.1)
	Diabetes mellitus	1.9 (1.4to2.6)
	Glomerulonephritis	2.1 (1.5to3.0)

[a] Abbreviations as in Table 1.

onset of microalbuminuria may prevent subsequent overt proteinuria and deterioration in renal function (15,16).

Second, a potentially cost-effective method for combating the current epidemic of ESRD might be to make available to first- and second-degree relatives of ESRD patients annual blood pressure screening, urinalysis (including microalbuminuria measurement in diabetic patients), serum creatinine determination, and counseling for avoidance of nephrotoxins. Because the vast majority of hypertensive subjects in the general population (17) and approximately 70% of diabetic patients (18) will never develop renal disease, such a targeted screening strategy might identify a greater proportion of hypertensive and diabetic patients who are at risk for ESRD (19).

Third, our observations extend previous studies that used strict entry criteria and limited the analyses to cases of ESRD with a predominantly hypertensive or diabetic etiology (5–9). Approximately 35 to 40% of African-American ESRD patients from Winston-Salem, NC, with carefully defined hypertension-(6) or type II diabetes mellitus-associated ESRD (7) had first-, second-, or third-degree relatives with ESRD. Twenty-six percent of whites with type II diabetes mellitus-associated ESRD from Winston-Salem reported close relatives with ESRD as well (9). Bergman *et al.* reported that 18 of 75 African-American index cases with hypertension-associated ESRD living in Birmingham, AL, had first-degree relatives with ESRD, and evidence for renal disease was present in 47% (35 of 75) of families (8). The investigators in North Carolina demonstrated that multiple etiologies of ESRD were frequently present in families (6). This was confirmed by the Alabama investigators (8). The initial family analyses used prevalent populations of ESRD patients. Prevalent study populations could bias the results if patient survival in familially clustered cases of ESRD was different from those in sporadically occurring cases. Therefore, although important, the results of these initial studies may not be applicable to general populations of dialysis patients in whom the etiologies of ESRD are more variable. The results of this analysis are more general because we analyzed all incident cases regardless of their eventual dialysis modality, and used the etiology of ESRD reported by the referring nephrologist; however, we recognize that the diagnosis in an individual case may not always be correct (20).

Our findings rely on the ability of patients to correctly identify a positive family history. In an attempt to collect DNA for genetic analysis from African-American sibling pairs concordant for ESRD, we contacted all 113 living siblings reportedly having ESRD from the 2649 African-American index cases in this data base. The family history was correct in 88% of these cases. Therefore, the prevalence of a family history in this group may have been slightly overestimated. We have no comparable data for Caucasian index patients; however, we consider it unlikely that the large racial differences in prevalence of family history that we observed can be accounted for solely by these kinds of misclassification errors.

Another application of the family history of ESRD data base includes identification of multiply affected families for genetic linkage analysis. Inherited, not environmental, risk factors appear to contribute strongly to the familial clustering of ESRD in African-Americans (17,21). Lei *et al.* recently demonstrated that the familial clustering of ESRD in African-Americans is in excess of what is expected based on the familial clustering of hypertension and diabetes mellitus in families (21). They suggested that genetic susceptibility increased the risk of developing the commonly reported etiologies of ESRD. We now have the potential to perform an efficient search for the genetic determinants of progressive renal failure (22–24). This may lead to the discovery of genetic markers for the early detection of individuals at risk. It is also possible that shared environmental influences may be responsible for some of the familial aggregation we have reported, and this possibility should be explored further (25).

Acknowledgments

The authors thank the physicians and staff members of the Southeastern Kidney Council (SEKC) (Raleigh, NC) dialysis facilities for their cooperation in completing the family history forms and Ms. Jenna Krisher, executive director of the SEKC, for assisting with data base creation and review of this manuscript.

References

1. United States Renal Data System: *USRDS 1994 Annual Data Report*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, August 1994
2. Whittle JC, Whelton PK, Seidler AJ, Klag MJ: Does racial variation in risk factors explain black-white differences in the incidence of hypertensive end-stage renal diseases? *Arch Intern Med* 151: 1359–1364, 1991
3. McClellan W, Tuttle E, Issa A: Racial differences in the incidence of hypertensive end-stage renal disease are not entirely explained by differences in the prevalence of hypertension. *Am J Kidney Dis* 12: 285–290, 1988
4. Bryne C, Nedelman J, Luke RG: Race, socioeconomic status, and the development of end-stage renal disease. *Am J Kidney Dis* 23: 16–22, 1994

5. Ferguson R, Grim CE, Opgenorth TJ: A familial risk of chronic renal failure among blacks on dialysis? *J Clin Epidemiol* 41: 1189–1196, 1988
6. Freedman BI, Spray BI, Tuttle AB, Buckalew VM Jr: The familial risk of end-stage renal disease in African Americans. *Am J Kidney Dis* 21: 387–393, 1993
7. Freedman BI, Tuttle AB, Spray BJ: Familial predisposition to nephropathy in African Americans with non-insulin-dependent diabetes mellitus. *Am J Kidney Dis* 25: 710–713, 1995
8. Bergman S, Key BO, Kirk KA, Warnock DG, Rostand SG: Kidney disease in the first-degree relatives of African Americans with hypertensive end-stage renal disease. *Am J Kidney Dis* 27: 341–346, 1996
9. Spray BJ, Atassi NG, Tuttle AB, Freedman BI: Familial risk, age at onset, and cause of end-stage renal disease in white Americans. *J Am Soc Nephrol* 5: 1806–1810, 1995
10. Southeastern Kidney Council, Inc., ESRD Network 6: *Annual Report, 1994*
11. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic Research: Principles and Quantitative Methods,* New York, Van Nostrand Reinhold, 1982, pp 179–249
12. Hosmer DW, Lemeshow S: *Applied Logistic Regression*, New York, John Wiley and Sons, 1989
13. Pettitt DJ, Saad MF, Bennet PH, Nelson RG, Knowler WC: Familial predisposition to renal disease in two generations of Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 33: 438–443, 1990
14. Seaquist ER, Geotz FC, Rich S, Barbosa J: Familial clustering of diabetic kidney disease: Evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med* 320: 1161–1165, 1989
15. Mathiesen ER, Hommel E, Giese J, Parving HH: Efficacy of captopril in postponing nephropathy in normotensive insulin-dependent diabetic patients with microalbuminuria. *Br Med J* 303: 81–87, 1991
16. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329: 1456–1462, 1993
17. Freedman BI, Iskandar SS, Appel RG: The link between hypertension and nephrosclerosis. *Am J Kidney Dis* 25: 207–221, 1995
18. Borch-Johnson K: Incidence of nephropathy in insulin-dependent diabetes as related to mortality. In: *The Kidney and Hypertension in Diabetes Mellitus*, edited by Mogensen CE, Boston, MA, Martinus Nijhoff, 1988, pp 33–40
19. Bergman SM, Key BO, Kirk KA, Rostand SG: First-degree relatives of African Americans with hypertensive-ESRD have lower ERPF and GFR associated with normal serum creatinine and urinalysis [Abstract]. *J Am Soc Nephrol* 7: 1577, 1996
20. Schlessinger SD, Tankersley MR, Curtis JJ: Clinical documentation of end-stage renal disease due to hypertension. *Am J Kidney Dis* 23: 655–660, 1994
21. Lei HH, Perneger TB, Klag MJ, Whelton PK, Coresh J: Is the association between family history of renal disease and end-stage renal disease explained by concurrent aggregation of risk factors? [Abstract] *J Am Soc Nephrol* 7: 1322, 1996
22. Yu H, Bowden DW, Spray BJ, Rich SS, Freedman BI: Linkage analysis between loci in the renin angiotensin axis and end-stage renal disease in African Americans. *J Am Soc Nephrol* 7: 2559–2564, 1996
23. Freedman BI, Yu H, Spray BJ, Rich SS, Rothschild CB, Bowden DW: Genetic linkage analysis of growth factor loci and end-stage renal disease in African Americans. *Kidney Int* 51: 819–825, 1997
24. Bowden DW, Sale M, Howard TD, Qadri A, Spray BJ, Rothschild CB, Akots G, Rich SS, Freedman BI: Linkage of genetic markers on human chromosomes 20 and 12 to NIDDM in Caucasian sib pairs with a history of diabetic nephropathy. *Diabetes* 46: 882–886, 1997
25. McClellan W: Hypertensive end-stage renal disease in blacks: The role of end-stage renal disease surveillance. *Am J Kidney Dis* 21[Suppl 1]: 25–30, 1993