Impact of Birth Weight on Familial Aggregation of End-Stage Renal Disease

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Key Words

Birth weight · End-stage renal disease ·
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Abstract

Background: Birth weight (BW) and family history (FH) of end-stage renal disease (ESRD) have been shown to have an independent association with development of subsequent ESRD. This study was undertaken to determine the effects of BW (low BW suggesting a congenital reduction in functional nephron number) on the observed familial aggregation of ESRD. **Methods:** Cases were identified from the ESRD Network 6 'Family History of ESRD' Study and BW was determined from birth certificate records maintained at the Office of Vital Records, South Carolina Department of Health and Environmental Control. BW and FH of ESRD data were available in 387 patients who initiated dialysis therapy between 1993 and 1997. Multiple logistic regression analysis was performed to assess the risk of low BW (<2,500 g) and high BW (≥ 4,000 g) on FH of ESRD. **Results:** A FH of ESRD in first or second-degree relatives was present in 24% of cases. No significant differences were observed in the frequency of a positive FH of ESRD in those with low BW compared to those with normal BW. There was a significant reduction in the prevalence of a FH of ESRD in those with high BW, compared to those with a normal BW (risk ratio 0.32, CI 0.11–0.94). **Conclusion:** The clustering of

either high BW or low BW within multiply affected ESRD families does not account for the observed familial aggregation of ESRD. In addition, high BW was associated with a reduced familial aggregation of ESRD.

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Introduction

The factors associated with the increasing incidence rates of end-stage renal disease (ESRD) in the United States remain unclear [1]. The increased risk among African Americans and residents of the Southeastern U.S. also remains an enigma [1]. Recent studies suggest that the racial and geographic disparities in ESRD, and the increasing incidence rates, may have a fetal origin as indicated by an association with birth weight (BW) [2, 3]. Diabetes and hypertension are the leading causes of ESRD and have been found to have an association with BW [4–6]. Brenner et al. [7] proposed a mechanism involving impaired kidney development in utero as an explanation for reduced renal function later in life. Such supplements of the Barker hypothesis are intriguing. However, the contribution of BW to traditional risk factors such as family history (FH) of ESRD, have yet to be clarified. Multiple studies have demonstrated that a FH of ESRD in first or second-degree relatives markedly increases an individual's risk for subsequent nephropathy [8–10].

This observational study assessed the relationship between BW and FH of ESRD. It is conceivable that families having multiple members with low BW, and potentially lesser numbers of functional nephrons, could manifest an increased familial aggregation of ESRD. Hence, there could be an association between FH of ESRD and BW. We attempted to determine whether individuals with a positive FH of ESRD were more likely to have a low BW or high BW compared to individuals lacking an FH of ESRD.

Methods

Study Population

The study cohort consisted of patients with ESRD who were born in South Carolina and participated in the ESRD Network 6 'Family History of ESRD' Study. Data collection for this study included extracting and linking information from two unique databases. The FH database includes incident dialysis patients registered in the Southeastern Kidney Council, Inc./ESRD Network 6 between September 1993 and November 1997 [11]. The FH information contained in this database has been shown to be highly accurate [11]. FH was considered positive if an ESRD patient reported having either a first- or second-degree relative with ESRD. For each patient who was born in South Carolina, BW was determined from the weight recorded on the South Carolina birth certificate. This information has been available since 1950. The identification data of these patients were sent to the Office of Vital Records at the South Carolina Department of Health and Environmental Control in Columbia, SC. A detailed data linking process has been described previously [2]. Low BW was defined as <2,500 g and high BW as $\geq 4,000$ g.

Statistical Analysis

Differences in patient populations were analyzed using χ^2 analysis or Student's *t* test. Multiple logistic regression was conducted to estimate the risk ratio of low and high BW on FH of ESRD, while adjusting for potential confounding factors. Significance testing was performed using two-tailed analysis, and $p < 0.05$ was considered significant.

Results

BW and FH of ESRD data were available in 387 patients. Table 1 presents the characteristics of the study group by FH. A positive FH of ESRD was present in 24.0% of cases (93/387). Of the 93 patients with a FH of ESRD, 84.9% (79/93) were African-American and 74.2% (69/93) were male. Age and gender were similar for patients with a positive FH and patients without a FH. Diabetes- and hypertension-associated ESRD reportedly accounted for 23.0% (89/387) and 36.4% (141/387) of the causes of ESRD, respectively. Among African-American

cases, 27.2% reported having a first- or second-degree relative with ESRD, compared to 14.6% of Caucasian cases ($p = 0.01$). The distribution of BW was similar between the two patient groups (12.9% low BW, 82.8% normal BW and 4.3% high BW amongst cases with a positive FH vs. 12.2% low BW, 75.5% normal BW and 12.2% high BW amongst cases without a FH of ESRD, $p = 0.09$).

Using a multiple logistic approach, high BW ($\geq 4,000$ g) was identified as having a significant protective effect on FH of ESRD (table 2). This analysis demonstrated that cases with low BW (<2,500 g) did not have a significant risk ratio for the familial clustering of ESRD relative to those with a normal BW (2,500–3,999 g) (risk ratio 0.89, CI 0.44–1.82). However, cases with a high BW had a significantly reduced risk ratio for familial aggregation of ESRD (risk ratio 0.32, CI 0.11–0.94). Race, gender, age at ESRD onset, cause of ESRD (diabetes vs. all others, hypertension vs. all others), and family size (number of first-degree relatives) were not significantly related to FH of ESRD (table 2).

Discussion

This study attempted to determine whether the familial clustering of ESRD is related to an inherited tendency toward having either a low or high BW. A familial clustering of low BW, if accompanied by a reduced number of functional nephrons, could be one potential explanation for the familial aggregation of ESRD. In the present study, the prevalence of a low BW did not differ significantly in ESRD cases with or without a FH of ESRD (12.9 vs. 12.2%, respectively). The results from multiple regression indicated that low BW had no effect on the risk of having a FH of ESRD. Therefore, the effects of low BW and FH of ESRD on risk for subsequent nephropathy appear to be independent. In this, and other reports, African-Americans more often have relatives with ESRD compared to whites [11]. However, multivariate analyses demonstrated that differences in patient race, gender and age did not alter the effect of low BW on the familial aggregation of ESRD (table 2).

The association between FH of ESRD and the increased risk for future ESRD has been well documented [11–16]. Potential explanations for this clustering include the sharing of specific genes, environmental exposures, and/or underlying physical disorders among family members [10, 17]. Diabetes and hypertension are independent risk factors for ESRD [1], but also have an association with FH [18, 19]. Epidemiological studies have identified a strong association of diabetes, hypertension, and ESRD

Table 1. Characteristics of the study population by family history of ESRD

	Positive family history (n = 93)	No family history (n = 294)	p ¹
Age, mean ± SE	37.7 ± 0.5	37.0 ± 0.8	0.43
Race, %			
Caucasian	14.6	85.4	0.01
African-American	27.2	72.8	
Gender, %			
Male	23.7	76.3	0.79
Female	25.0	75.0	
Primary causes, %			
Diabetes	21.4	78.6	0.77
Hypertension	25.5	74.5	
Other	24.2	75.8	
BW, %			
<2,500 g	25.0	75.0	0.09
2,500–3,999 g	10.0	90.0	
≥ 4,000 g	25.8	74.8	
BW, g, mean ± SE	3,150.7 ± 60.1	3,230.1 ± 36.4	0.28
Family size ² , mean ± SE	7.9 ± 0.4	7.0 ± 0.2	0.06

¹ χ^2 analysis or Student's t test.

² Number of first-degree relatives in the family.

among adults with low and high BW [2, 21, 22]. Animal studies reveal that a congenital reduction in nephron number is associated with enhanced susceptibility to hypertension with an acceleration in age-related proteinuria and glomerulosclerosis [23–26]. Human studies confirm that the kidneys in growth-retarded infants are smaller and contain fewer nephrons than do those in normal-sized infants [27, 28]. Brenner and colleges have suggested that a congenital reduction in nephron number is an unappreciated risk factor for the development of adult systemic hypertension [29]. Although low BW clearly predisposes to the development of ESRD, our results suggest that it does not appear to account for the widely reported familial clustering of kidney failure.

We also observed a markedly reduced risk of familial clustering of ESRD in cases having a high BW ($\geq 4,000$ g). In cases with a high BW, the sporadic nature of ESRD suggests that familial (or inherited factors) are not associated with the development of ESRD. These findings are consistent with a high BW predisposing to development of diabetes mellitus per se, independent from the risk for nephropathy.

BW data have only been included on birth certificates in South Carolina since 1950. This logistical constraint re-

Table 2. Risk ratios of BW on family history of ESRD (n = 387)

Variable	Risk ratio (95% CI) ¹
BW ²	
<2,500 g	0.89 (0.44, 1.82)
2,500–3,999 g	1.0
≥ 4,000 g	0.32 (0.11, 0.94)
Race	
Caucasian	1.0
African-American	1.91 (0.97, 3.76)
Gender	
Male	1.0
Female	1.07 (0.61, 1.88)
Age at ESRD onset	1.01 (0.98, 1.05)
Primary causes	
Other	1.0
Hypertension	0.90 (0.51, 1.58)
Diabetes	0.89 (0.46, 1.72)
Family size ³	1.03 (0.97, 1.10)

¹ Multiple logistic regression using negative family history of ESRD as reference group.

² Low BW defined as <2,500 g and high BW as $\geq 4,000$ g.

³ Number of first-degree relatives.

stricted our study group to relatively young adults and limited our sample size. However, understanding the causes of ESRD that develops in a young population was a major objective. It is also clear that younger dialysis patients manifest greater degrees of familial aggregation of ESRD than do older patients on dialysis [11]. The sample size in this report was relatively small (387 cases) and likely reduced the statistical power. However, these are unique data that were created by combining information from 2 large databases. ESRD Network 6 is the only ESRD Network that currently maintains a 'FH of ESRD' database in all incident dialysis patients. South Carolina was one of the first states to include BW data on their birth certificates. Importantly, no trends toward a significant relationship between a low BW and FH of ESRD were observed. In the future, it would be ideal if larger databases became available to address this relationship. However, these initial results strongly support the contention that BW and FH of ESRD are independent risk factors for subsequent nephropathy.

The effect of a change in body habitus, or pre-dialysis body mass index (BMI) relative to BW, may also impact the risk of a FH of ESRD. It has been suggested that those with a low BW who become obese later in life may have an increased risk of developing diabetes mellitus [18]. Pre-dialysis BMI data were available in 61% of cases (236/387). Logistic regression analysis including pre-dialysis

BMI in these 236 cases failed to alter the relationship between low BW and FH of ESRD (data not shown). Therefore, we conclude that pre-dialysis BMI (i.e. change in body habitus) does not impact the effect of a low BW on the FH of ESRD.

The results of this study suggest that the inherited and environmental factors that contribute to a low BW are independent from those that cause the familial aggregation of ESRD. The observation that high BW reduces the familial aggregation of ESRD supports the continued investigation of the mechanism(s) of fetal and early life exposure on risk for subsequent ESRD.

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