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Low birth weight is associated with earlier onset of end-stage renal disease in Danish patients with autosomal dominant polycystic kidney disease

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Low-birth-weight individuals have a higher risk of hypertension and end-stage renal disease (ESRD). Here we investigated whether low birth weight was associated with earlier onset of ESRD in patients with autosomal dominant polycystic kidney disease (ADPKD). In collaboration with all Danish departments of nephrology, 307 of 357 patients with ADPKD and ESRD born and living in Denmark were recruited. We were able to analyze complete data of 284 patients obtained from both hospital medical files and midwife protocols in the Danish State Archives. Multivariable linear regression adjusted for birth weight, adult height, mean arterial pressure, gender, birth decade, and type of antihypertensive treatment showed that for every kilogram increase in birth weight, the age at onset of ESRD significantly increased by 1.7 years. Male gender and increased mean arterial pressure were both associated with earlier onset of ESRD. Patients treated with renin–angiotensin system blockade or calcium channel blockers during follow-up had significantly later onset of ESRD by 4.3 years and 2.1 years, respectively. Treatment with beta-blockade or a diuretic was not associated with the age at onset of ESRD. Thus, low birth weight may contribute to considerable phenotypic variability in the progression of renal disease between individuals with ADPKD.

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Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disease estimated to affect around 4–6 million people worldwide.[1] With the growth of renal cysts the renal function gradually deteriorates, and 6% of all patients starting renal replacement therapy in Denmark had ADPKD in the year 2009.[2] Mutations in the *PKD1* gene are found in ~85% of the patients with ADPKD and these patients on average reach end-stage renal disease (ESRD) about 20 years earlier than the patients with mutations in the *PKD2* gene (54.3 vs. 74.0 years).[3,4] Despite adjustment for genotype and other factors associated with severe progression in ADPKD, the often considerable variability in renal disease progression found within families with ADPKD is still largely unexplained.[5]

Nephrogenesis begins during the 9th week of gestation and continues up through the 36th week where it ends, and the number of nephrons is dependent on both gestational age and growth conditions *in utero*.[6] The Brenner hypothesis suggested that intrauterine growth restriction results in low birth weight (LBW), low nephron mass, and thereby an increased risk of developing hypertension and renal disease.[7] Today studies have shown that LBW is associated with a reduced number of enlarged glomeruli,[8–10] salt sensitivity of blood pressure, microalbuminuria, and low glomerular filtration rate.[11–14] Further, children with minimal change nephropathy, nephrotic syndrome or IgA nephropathy, and birth weights <2500 g have an adverse renal outcome compared with normal birth weight children.[15–18] Two case–control studies and a large cohort study have shown that individuals with birth weight <2500 g have a 40–70% increased risk of developing ESRD irrespective of gender and race.[19–21]

Whether LBW contributes to the renal disease variability in individuals with ADPKD has, to our knowledge, never been investigated. The primary objective of this study was therefore to investigate whether LBW is associated with the younger age at onset of ESRD in individuals with ADPKD. Second, it was investigated whether other potential risk factors influenced disease progression in ADPKD.

RESULTS

In a national collaboration with all Danish departments of nephrology, 307 patients or 86% of the population with

Table 1 | Clinical characteristics of study population

	Both	Men	Women
No. of patients	284	152	132
Follow-up (year), median (IQR)	4.8 (1.9–8.6)	4.2 (1.5–7.4)	5.5 (2.4–10.2)
Age at ESRD (year), mean (s.d.)	54.1(9.9)	53.4 (10.3)	54.9 (9.3)
Hypertensive (%)	262 (94.9)	140 (94.6)	122 (95.3)
MAP, mean (s.d.)	108.4 (8.9)	109.4 (9.5)	107.5 (8.0)
Users of RAS blockade (%)	69.0	71.1	66.7
Users of beta-blockade (%)	58.4	62.5	53.5
Users of calcium channel blockers (%)	68.0	74.3	60.5
Users of diuretics (%)	80.4	79.6	81.4
No antihypertensive treatment (%)	5.7	6.6	4.7
Potential risk factors			
Pyelonephritis (%)	24.6	15.8	34.6
Smoking (%)	50.0	60.6	37.9
Birth weight (kg), mean (s.d.)	3.537 (594)	3.606 (624)	3.458 (550)
Distribution of birth weights			
$<$2500 g, No. of patients (%)	9 (3.2)	4 (2.6)	5 (3.8)
2500–2999 g, No. of patients (%)	31 (10.9)	16 (10.5)	15 (11.3)
3000–3499 g, No. of patients (%)	81 (28.4)	40 (30.1)	41 (27.0)
3500–3999 g, No. of patients (%)	99 (34.7)	45 (29.6)	54 (40.6)
$\geqslant$4000 g, No. of patients (%)	65 (22.8)	46 (30.3)	19 (14.3)

Abbreviations: ESRD, end-stage renal disease; IQR, interquartile range; MAP, mean arterial pressure; RAS, renin–angiotensin system.
Follow-up is from first hospital contact documented in the medical records to onset of ESRD. Hypertensive patients had either a mean arterial pressure $>$107 mm Hg (blood pressure 140/90) or used an antihypertensive drug during follow-up. Patients on RAS blockade used either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

ADPKD and ESRD were included. Of these, 284 patients had sufficient available data for the analyses. The year at onset of ESRD ranged from 1970 to 2008 with a median of 2002. Each patient was registered from first documented hospital contact to the onset of ESRD with an average follow-up period of 4.8 years, and the clinical characteristics are outlined in Table 1. Females were followed for a longer time period before the onset of ESRD compared with males (5.5 years vs. 4.2 years; $P=0.03$). In the unadjusted analysis (Table 1), there were no differences between males and females in the average age at onset of ESRD, the percentage with hypertension, the mean arterial pressure (MAP), or the percentage of patients on either an ACE inhibitor or an angiotensin receptor blocker (renin–angiotensin system (RAS) blockade). One or more episodes of pyelonephritis was more often found in females compared with males (34.6 vs. 15.8%; $P=0.0002$). As expected males were taller than females ($P<0.0001$) and a higher percentage of males had a self-reported use of tobacco ($P=0.0002$; Table 1).

On the basis of a questionnaire answered by each patient, information on birth weight was found in 95% of all patients in the midwife protocols stored in the Danish State Archives. Male babies had on average a larger birth weight compared with female babies (3606 vs. 3458 g; $P=0.04$). Of the 284 patients with a reported birth weight, 73 had an affected father, 81 had an affected mother, and in the remaining 130 patients the parental affection status was unknown. In the 154 individuals where the affected parent had been reported there were no difference in the average birth weight between patients with an affected father vs. mother (3561 vs. 3494 g; $P=0.49$).

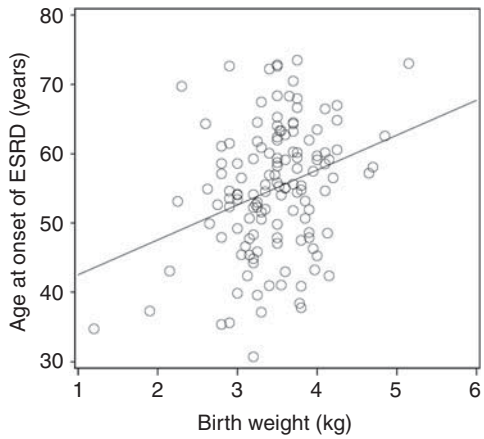

Figure 1 | Correlation between birth weight and age at onset of end-stage renal disease (ESRD) in 132 Danish women with autosomal dominant polycystic kidney disease. With every kilogram increase in birth weight, the age at onset of ESRD increased by 5.0 years, $r=0.30$ and $P=0.0005$ (unadjusted analysis).

The unadjusted associations between birth weight and age at onset of ESRD are outlined for women in Figure 1 and men in Figure 2 with ADPKD. The regression lines show how the age at onset of ESRD increased by 5.0 years in the 132 women and 3.9 years in the 152 men by every kilogram increase in birth weight. The two correlation coefficients were $r=0.30$ in Figure 1 ($P=0.0005$) and $r=0.24$ in Figure 2 ($P=0.004$).

Information on ethnicity, proteinuria, and ADPKD genotype was not available. However, the included patients