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Variables affecting adolescent renal function in patients born with vesico-ureteric reflux

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KEYWORDS

Vesico-ureteric reflux;
Kidney function;
Birth weight

ABBREVIATIONS

BP, blood pressure;
CrCl, creatinine clearance;
FeNa, fractional excretion of sodium

Abstract ***Objective:*** To examine whether factors in a child's perinatal history influence renal function in adolescence, using a cross-sectional study, as during the past two decades researchers have tried to ascertain whether factors such as low birth weight might be related to a decline in kidney function in adolescence, although published data for children born with vesico-ureteric reflux (VUR) remain insufficient.

Patients and methods: Sixty-one children (20 boys and 41 girls), born between 1985 and 1989 in Greece and diagnosed with VUR, were assessed. A detailed personal and family history was taken and basic anthropometric variables were measured. Kidney function was calculated from serum creatinine levels, and the glomerular filtration rate (GFR), fractional excretion of sodium, albumin levels in urine, creatinine clearance, cystatin C level and the dimensions of each kidney were measured.

Results: The results showed a positive relationship of birth weight ($P = 0.01$) with blood pressure in adolescence in children diagnosed with any degree of VUR. Renal function seemed to be intact whatever the cause of VUR, the volume of the kidneys in adolescence ($P = 0.386$ and 0.483, respectively, for the right and

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left kidney) and the values of GFR ($P = 0.105$), creatinine clearance ($P = 0.213$) and cystatin C ($P = 0.055$).

Conclusions: These results showed that although there is a positive association between blood pressure in adolescence and birth weight, in children born with VUR there was no deterioration in renal function. Kidneys seem to function normally regardless of the gestational age at birth.

Introduction

Since the beginning of the 19th century several human and animal studies have been published showing a direct association between birth weight, nephron number [1] and chronic diseases in adulthood such as coronary heart disease, hypertension and diabetes [2–5]. With the improved statistical procedures and level of medical-record keeping, this hypothesis is now strongly disputed.

The purpose of the present study was to assess the possible effects of some confounding factors, like those noted above, on renal function in adulthood, in children born with VUR and diagnosed either during routine prenatal testing or after having a UTI such as cystitis.

Patients and methods

The study included 61 adolescents (20 boys and 41 girls, aged 18–24 years) in whom any degree of VUR was diagnosed in the neonatal period, either due to a febrile UTI, prenatal investigation or any other cause such as cystitis. Their gestational age, birth weight, degree of VUR and the presence or not of a febrile UTI, its duration and possible impaired kidney function that might be detected using a DMSA scan, were obtained from routine neonatal records.

All patients had an appointment for a clinical and laboratory examination. Anthropometric measurements included blood pressure (BP), which was taken three times per day for 3 days before the appointment, and the mean BP then used in the study. The height of the patients (while barefoot) was measured and they were weighed using an electronic scale.

All patients had a laboratory examination which included measurements of serum creatinine, creatinine clearance (CrCl), GFR, fractional excretion of sodium (FeNa) and cystatin C, as markers of kidney function. From a 24-h urine collection we measured a1-globulin, b2-microglobulin and the possible presence of leukocyturia, which can indicate a progressive deterioration of renal function. The volume, width, length and thickness of the kidneys were calculated using ultrasonography.

The variables were assessed using multiple regression analysis, with BP as the dependent variable and gender, current age, weight at birth, gestational age, the degree of VUR in each kidney, kidney function as assessed by the DMSA scan, the presence or not of a febrile UTI, the volume of each kidney and renal biochemistry, as independent variables.

Results

We first assessed the association between BP and all the variables listed above, both clinical and laboratory, taking into account not only measurements from the neonatal history, such as birth weight, height and gestational age, but also measurements from the current medical condition, e.g., current height, weight and the laboratory results. The purpose was to identify which perinatal factors, including VUR, might cause defective kidney function in adolescence and whether this is reflected, e.g., in an increased BP or pathological renal biochemistry.

Table 1 summarises the general characteristics of the study population. The mean age was ≈ 20 years, the mean birth weight was 2.56 kg and the gestational age

Table 1 The general characteristics of the patients.

Variable (*n*)	Mean (SD, range), or *n* (%)
Age, years (61)	19.7 (1.68, 18–24)
Birth weight, kg (61)	2.56 (0.87, 1–4)
Gestational age, days (60)	35.3 (4.1, 25–41)
Gender	
Male	20 (32.8)
Female	41 (67.2)
VUR	
Degree of VUR	
Left kidney	
0	14 (23)
1	2 (3)
2	8 (13)
3	19 (31)
4	15 (25)
5	3 (5)
Right kidney	
0	19 (31)
1	3 (5)
2	6 (10)
3	17 (28)
4	12 (20)
5	4 (7)

Table 2 Tests of between-subjects effects by regression with the dependent variable of systolic BP or kidney volume and the parameter estimates of regression analysis.

Variable	BP			Kidney volume
	Regression *P*	B (SE)	95% CI	Regression *P*
Corrected model	0.248*			0.091†
Intercept	0.002	221.2 (65.25)	88.99–353.42	0.011
Age	0.658	0.418 (0.938)	−1.48–2.32	0.394
Weight at birth	0.001	23.25 (6.69)	9.69–36.8	0.332
Gestational age	0.002	−4.89 (1.43)	−7.78 to −1.99	0.388
Current weight	0.151	0.324 (0.22)	−0.124–0.773	0.568
Current height	0.913	−0.031 (0.284)	−0.607–0.544	0.740
Febrile UTI	0.442	−2.93 (3.77)	–10.58–4.71	0.456
VUR left	0.259	−1.33 (1.16)	−3.69–1.02	0.013
VUR right	0.530	−0.729 (1.15)	−3.06–1.60	0.353
DMSA right	0.637	0.077 (0.161)	−0.250–0.403	0.134
DMSA left	0.838	0.034 (0.167)	−0.305–0.374	0.528
Kidney volume				
Right	0.386	–0.101 (0.115)	−0.333–0.132	–
Left	0.483	0.092 (0.129)	−0.170–0.353	–
Creatinine	0.117	−8.29 (5.17)	−18.77–2.18	0.468
CrCl	0.213	0.083 (0.065)	−0.050–0.216	0.914
GFR	0.105	−8.16 (4.91)	−18.12–1.794	0.264
FeNa	0.918	−0.799 (7.73)	−16.46–14.87	0.526
a1-Globulin	0.427	0.549 (0.684)	−0.837–1.94	0.633
b2-Microglobulin	0.268	6.14 (5.47)	−4.93–17.23	0.720
Cystatin C	0.055	−15.05 (7.60)	−30.45–0.359	0.578
Microleukocyturia	0.111	−0.156 (0.095)	−0.349–0.037	–
Leukocyturia	0.177	0.667 (0.485)	−0.315–1.65	0.074
Gender	0.558	3.48 (5.89)	−8.45–15.40	–
Systolic BP				0.844

* $r^2 = 0.432$.
† 0.439.

was 36 weeks. Two-thirds of the patients were girls (67%). The degree of VUR in each kidney is also given in Table 1.

Table 2 shows the results of multiple regression analysis, without adjustment for current height and weight, to predict which of the variables measured in adolescents born with any degree of VUR might affect the BP later in life; these variables are known factors that might alter BP.

Table 2 also shows parameter estimates and constant values of each parameter. The results show that BP in adolescence is positively related to birth weight ($P = 0.01$) and negatively related to gestational age ($P = 0.02$). Increased BP seems neither to be the cause of impaired kidney function, as indicated by renal biochemistry, nor a result of a higher body mass index as indicated by current weight and height ($P = 0.151$ and 0.913, respectively).

Several studies show a direct and inverse correlation between birth weight, glomerular and kidney volume [6–9]. It is widely accepted and confirmed by renal biopsy that the existing glomeruli must undergo compensatory hypertrophy and hyperfiltration to sustain adequate renal function, an adaptation that might hasten the loss of existing glomeruli and accelerate a decline in renal function. Table 2 shows that kidney dilatation (if present) is irrelevant for kidney function and the presence or not of VUR ($P > 0.1$). Thus kidneys seem to be able to fully compensate their function in adolescence without dimensional or functional disturbances.

Discussion

Reflux nephropathy is positively correlated with high intravesical pressure and chronic diseases in adulthood [10–12]. The preferred technique for the initial diagnosis of reflux nephropathy and renal scarring is ^{99m}Tc-DMSA renal scintigraphy (sensitivity 92%, specificity 98%), while the use of ultrasonography is a reliable, cheap and quick examination to monitor kidney growth over time. Children with reflux nephropathy should be engaged in a nephrological follow-up protocol, as the complications can take 10–20 years to develop [13]. Uncontrollable arterial hypertension and leukocyturia are widely accepted predictors of poor prognosis.

In Britain in the early 20th century, populations with the highest rates of neonatal mortality were associated with the highest rates of coronary heart disease later in life [14]. This observation was the most important stimulus for the ‘fatal origins’ [15] hypothesis of adult

disease. In 1981, a study by Simpson et al. [16] in New Zealand reported a negative association between birth weight and BP, and in the following decades several similar reports were added to this observation, led by Barker et al. [14], that supported the hypothesis that there is a direct association between birth weight, nephron number and chronic diseases in adulthood such as coronary heart disease, hypertension and diabetes [17–19]. This hypothesis seems to have been largely accepted worldwide from the end of the 20th century, when more exact statistical procedures were developed and electronic medical-record keeping was used by most hospitals.

The 'foetal origins' hypothesis initially postulated that foetal under-nutrition during early gestation results in a raised BP during adulthood. As reported in 1996 in a review of multivariate regression coefficients from 28 studies [20], it was estimated that a 1-kg higher birth weight is typically associated with a 2–4 mmHg lower systolic BP. Whereas almost all of the available regression coefficients had been adjusted for measures of current weight when BP was assessed, few involved an adjustment for other potential confounding factors that might be present and interfere with the final results. Such confounding factors are, e.g., height at birth, the presence of congenital kidney defects such as polycystic kidney or VUR, and gestational age. These factors are well known to cause a lower nephron number and subsequent higher BP, regardless of the final birth weight.

Nonetheless, the birth weight depends not only on the gestational age and any intrauterine growth restriction, but also on the socio-economic status of the mother and, hence, of the environment into which a baby is born and is likely to be raised. Thus, the separation of birth weight from the social circumstances that are strongly associated with it would probably be difficult. These factors are not easily measured or simulated to allow statistical analysis, so in the present study we considered only measurable factors that might influence renal function. In particular we assessed variables related to somatic growth, such as height and weight, the degree of VUR, and current renal biochemistry.

The results of our study showed that adolescents born with any degree of VUR can have hypertension, but this is negatively related to gestational age and positively only to birth weight. These results disagree both with the initial hypothesis of Barker et al. [14], and a recent report [21], which found a moderate decrease in renal volume and function, but seem to agree with the hypothesis that kidney volume is irrelevant to hypertension or proteinuria later in life. Although difficult data to collect, more patients born with VUR are needed to provide valid statistically significant results in such studies. From our survey we conclude that kidneys, even with fewer nephrons, managed to completely compensate in adulthood without a deterioration of renal function. This finding provides evidence that hypertension might be due to secondary factors, as noted above. Our analysis was carried out after controlling as much as possible for the factors related to the dynamics of BP without statistical adjustment, giving each variable the same statistical significance in the regression analysis.

Although the present research was carefully organised and analysed, there are limitations and shortcomings. There were relatively few patients (only 61) and they might not be representative of most children born with VUR. Thus, more patients are needed, but this would require the co-ordination of all the paediatric hospitals in Greece. The measurement of BP was not an ambulatory assessment, which is better than office measurements of BP for identifying patients with hypertension, and lastly, we did not take into account confounding factors such as socio-economic status and the lifestyle of each family, as these are difficult to measure and analyse objectively.

Conflict of interest

None.

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