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Renal Concentrating Capacity is Linked to Blood Pressure in Children with Autosomal Dominant Polycystic Kidney Disease

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Summary

Impaired glomerular filtration rate (GFR) is a risk factor for the development of hypertension in patients with autosomal dominant polycystic kidney disease (ADPKD). However, markers of tubular function were not tested whether they are linked to hypertension or blood pressure (BP) level. The aim of our study was to investigate the relationship between renal concentrating capacity and BP in children with ADPKD. Fifty-three children (mean age 11.8±4.4 years) were investigated. Standardized renal concentrating capacity test was performed after nasal drop application of desmopressin, BP was measured by ambulatory BP monitoring (ABPM). Renal concentrating capacity was decreased in 58 % of children. The prevalence of hypertension was significantly higher in children with decreased renal concentrating capacity (35 %) than in children with normal renal concentrating capacity (5 %) ($p<0.05$). Significant negative correlations were found between renal concentrating capacity, ambulatory BP and number of renal cysts ($r = –0.29$ to $–0.39$, $p<0.05$ to $p<0.01$). In conclusion, the concentrating capacity is decreased in about half of the patients and is linked to BP. Decreased renal concentrating capacity should be considered as an early marker of functional impairment in ADPKD and a further risk factor for hypertension.

Key words

Renal concentrating capacity test • Autosomal dominant polycystic kidney disease • Blood pressure • Hypertension • Children

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) with its incidence 1:1000 is the most common inherited chronic renal disease leading to end-stage renal failure in adults (Gabow 1993). It is primary a tubular disorder characterized by progressive cystic degeneration of the kidney mainly of the distal tubule. It affects not only adult patients but significant morbidity exists already in childhood (Fick *et al.* 1994, Sharp *et al.* 1998). Renal concentrating capacity is a simple functional marker of the distal tubule that is decreased in approximately 50 % of pediatric patients with ADPKD (Kääriäinen *et al.* 1988).

Arterial hypertension, which is a complication of ADPKD in adult as well as in pediatric patients, contributes to the progression of the disease as well to the cardiovascular morbidity and mortality of the patients

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(Fick *et al.* 1994, Marcelli *et al.* 1995, Seeman *et al.* 1997, Sharp *et al.* 1998). The pathogenesis of hypertension in ADPKD is complex and includes activation of the renin-angiotensin system, sodium retention or alteration of vasoconstrictor and vasodilator systems (Bell *et al.* 1988, Marcelli *et al.* 1995, Merta *et al.* 2003). There are several known risk factors for development of hypertension such as mutation in PKD1-gene, male gender, decreased glomerular filtration rate (GFR), early onset of the disease or more advanced structural abnormalities of the kidney (Bell *et al.* 1988, Gabow *et al.* 1990, 1992, Seeman *et al.* 2003). On the contrary, there are no data in the literature about the impairment of tubular function as a risk factor for the development of hypertension in patients with ADPKD.

The aim of our study was to investigate the relationship between renal concentrating capacity, blood pressure (BP) and renal structure in a population of children and adolescents with ADPKD and normal GFR who were off antihypertensive medication.

Methods

Fifty-three children and adolescents (27 boys) originating from 43 families with ADPKD were investigated, 14 patients were described in our earlier paper (Seeman *et al.* 1997). The diagnosis of ADPKD was established on the basis of a positive family history combined with characteristic ultrasound features (at least two renal cysts altogether according to Ravine *et al.* (1994). The mean age at the time of the study was 11.8±4.4 (range 3.4-19.4) years. Twenty-three children were asymptomatic at the time of the study, in 30 children the following signs or symptoms were noted in their past medical history: hypertension by casual BP measurements (14 children), headache (13), flank or abdominal pain (12), urinary tract infection (8 children: 6 children cystitis, 2 children pyelonephritis), enuresis (3), proteinuria (2), gross hematuria (1), microhematuria (1) and palpable abdominal masses (1). More than one symptom in a single child is possible.

Standardized renal concentrating capacity test was performed early in the morning by measuring urine osmolality 4 hours after nasal application of 5 μg/5 kg body weight 1-deamino-8-D-arginine-vasopressin – desmopressin (DDAVP, Ferring, Czech Republic, see Janda *et al.* 1988). The intake of fluids was stopped throughout 4 hours of the study and urine osmolality was measured in urine collected during this period (urine osmolality was determined from the depression of freezing point using Roeblig osmometer and expressed in mOsmol/kg). No child suffered from rhinitis at the time of the study. We observed no complications during the test. Decreased renal concentrating capacity was defined as urine osmolality < 900 mOsmol/kg (Janda *et al.* 1988).

Blood pressure was measured by ambulatory blood pressure monitoring (ABPM) during 24 hours using a SpaceLabs 90207 (Redmond, Washington, USA) oscillometric monitor one day before the renal concentrating capacity test to avoid possible influence of DDAVP on BP. Blood pressure was automatically recorded every 20 min during the daytime and every 30 min at night. A protocol was obtained on the activities during ABPM. Mean BP during daytime and at night were calculated and compared with standards obtained in healthy European children and adolescents of the same sex and height (Soergel *et al.* 1997). Individual BP values were expressed as standard deviation score (SDS) from the mean of normal children corrected for height, according to following formula $SDS = (X - X50): SD50$, where X is the individual's measurement, $X50$ is the mean in the healthy population and $SD50$ is the standard deviation of the normal population mean. Hypertension was defined as a mean systolic and/or diastolic BP during daytime and/or nighttime ≥ 95th percentile for normal pediatric population (Soergel *et al.* 1997). For the expression of BP data in children < 115 cm body height (data not expressed in the study done by Soergel *et al.* 1997), the extrapolation of the BP percentile from the groups of children with higher body weight was used (Soergel, personal communication). No patient was treated with antihypertensives at the time of the study.

All patients have normal GFR according to the Schwartz formula (Schwartz *et al.* 1987), mean GFR was 113±19 ml/min/1.73 m^2 (range 80-168), serum creatinine was measured using a standard method (enzymatic, Bayer).

Renal ultrasonography was performed using a Toshiba 270 SSA Japan instrument. The kidney length and kidney volume were evaluated and compared with normal standards (Dinkel *et al.* 1985), expressed as standard deviation scores (SDS). The number of cysts was determined in each patient pooled for both kidneys.

The data were expressed as means and standard deviation and were analyzed using Student's t-test for random samples. Means of the variables were compared using the two samples t-test for unequal sample sizes. Correlations between parameters were calculated using

the SPSS statistical program, $p<0.05$ values were considered as statistically significant.

Results

Renal concentrating capacity was decreased in 31 patients (58 %). Mean urine osmolality was 882±341 (range 390-1118) mOsmol/kg. Data of individual patients are given in Figure 1.

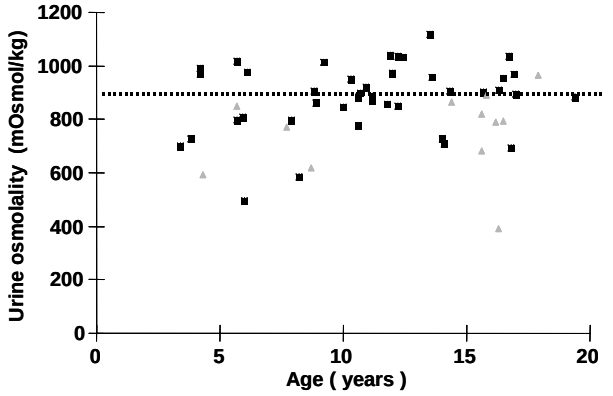

Fig. 1. Renal concentrating capacity in 53 children with ADPKD (dotted line represents the lower limit of normal concentrating capacity, squares represent normotensive children, triangles represent hypertensive patients)

Twelve children (23 %) were defined as hypertensive and 41 as normotensive. The prevalence of hypertension was significantly higher ($p<0.05$) in children with decreased renal concentrating capacity (11 of 31 children, 35 %) than in children with a normal renal concentrating capacity (1 out 22 children, 5 %). The mean daytime systolic BP was 0.2±1.1 SDS, mean daytime diastolic BP was –0.3±1.1 SDS, mean night-time systolic BP was 0.3±1.0 SDS and mean night-time diastolic BP was 0.2±1.1 SDS. There was a significant difference between the renal concentrating capacity in children with hypertension compared to children with normal blood pressure (793±150 mOsmol/kg in hypertensive children vs. 901±129 mOsmol/kg in normotensive patients, $p<0.05$).

Correlations between renal concentrating capacity and BP, renal structure and GFR are shown in Table 1. The correlations with BP were significant either when studied during daytime or at night. As an example, correlation between renal concentrating capacity and daytime systolic BP is shown in Figure 2. The correlations with ultrasonographic parameters of the kidneys were significant only for the number of renal cysts (Table 1, Fig. 3).

Table 1. Correlations of renal concentrating capacity with systolic BP, diastolic BP, renal structural parameters and GFR in children with autosomal dominant polycystic kidney disease

	Renal concentrating capacity (mOsmol/kg)	
Daytime systolic BP (SDS)	r = –0.39	p<0.01
Daytime diastolic BP (SDS)	r = –0.29	p<0.05
Nighttime systolic BP (SDS)	r = –0.37	p<0.01
Nighttime systolic BP (SDS)	r = –0.29	p<0.01
Renal volume (SDS)	r = –0.10	NS
Renal length (SDS)	r = –0.09	NS
Number of renal cysts (in both kidneys)	r = –0.39	p<0.01
Creatinine clearance (ml/min/1.73 m^2)	r = –0.29	p<0.05

BP – blood pressure, SDS – standard deviation score, r – correlation coefficient, NS – not significant

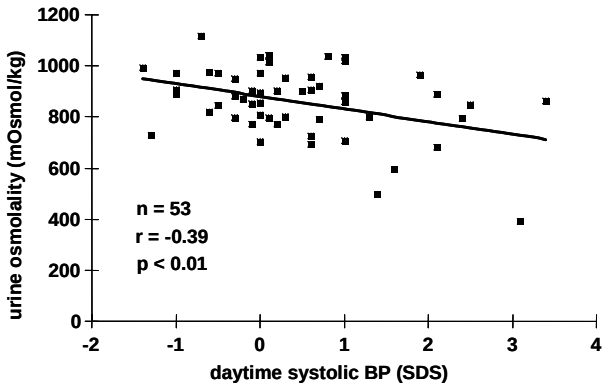

Fig. 2. Correlation between renal concentrating capacity and daytime systolic BP in children with ADPKD

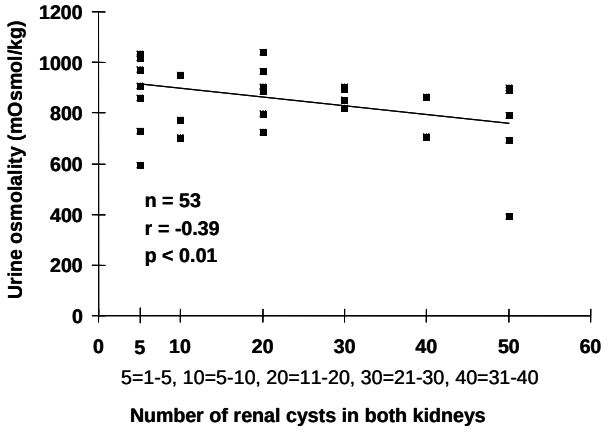

Fig. 3. Correlation between renal concentrating capacity and number of renal cysts in children with ADPKD

Discussion

Autosomal dominant polycystic kidney disease is a common and serious disease leading to chronic renal failure in adults (Gabow 1993). Arterial hypertension is a common complication of ADPKD which affects about 60-75 % of adult patients with ADPKD before glomerular function is impaired (Marcelli *et al.* 1995, Chapman and Gabow 1997), but can also be detected in 5-44 % of children (Sedman *et al.* 1987, Kaplan *et al.* 1989, Gagnadoux *et al.* 1989, Zerres *et al.* 1993, Fick *et al.* 1994, Sharp *et al.* 1998). Hypertension is not only a strong risk factor for cardiovascular morbidity and mortality but also a potent risk factor for the progression of chronic nephropathies (Guidelines Committee 1999).

In a previous study (Seeman *et al.* 2003), we applied ambulatory blood pressure monitoring (ABPM) in a group of mostly asymptomatic children with ADPKD and normal GFR and found that ambulatory blood pressure correlates with renal structure (renal volume, renal length and number of renal cysts) but not with creatinine clearance, total proteinuria or microalbuminuria – markers of glomerular function or glomerular injury. However, ADPKD is primarily a tubular disorder affecting primary distal tubule at early stages of the disease. Therefore we have hypothesized that BP in ADPKD patients could be related to the tubular function. Renal concentrating capacity test is a simple, routine and valuable method for investigating function of the distal tubule and collecting duct (Janda *et al.* 1988, Marild *et al.* 2001).

Renal concentrating capacity in children with ADPKD was previously investigated in one small study on 10 children only (Kääriäinen *et al.* 1987). In this study the concentrating capacity was decreased in 57 % of children. Our present study on a substantially larger cohort of 53 patients confirmed these results by showing a decreased concentrating capacity in 58 % children. Furthermore, we clearly demonstrated in this study that renal concentrating capacity is related to BP. We chose ABPM for BP measurements because it is a more adequate method than casual BP measurements when investigating BP changes in adults as well as in children and adolescents (Sorof and Portman 2000). We have not only shown that hypertensive children have a worse renal concentrating capacity than normotensives, but also we have found a significant correlation between the concentrating capacity and ambulatory BP values. This relationship was evident for daytime as well as for nighttime BP and was more powerful for systolic than for diastolic BP. Systolic BP is currently regarded as a better prognostic factor than diastolic BP especially in adolescents, young adults and the elderly (Guidelines Committee 1999, Sorof 2001).

We have also shown that the number of renal cysts but surprisingly not the renal length or volume correlated with the renal concentrating capacity. This finding demonstrates that a high number of cysts, a structural marker of the severity of this progressive disease, is associated with a decreased concentrating capacity, a functional marker of tubular impairment. The number of renal cysts also correlated with BP in our previous study (Seeman *et al.* 2003). All these findings unequivocally demonstrate that there is a link between renal structural abnormalities (number of renal cysts and renal size), tubular function (renal concentrating capacity) and the blood pressure. The exact pathogenesis of hypertension in patients with ADPKD is not yet clear. However, the increased number of renal cysts (associated in our study with decreased renal concentrating capacity) resulting in local renal ischemia and activation of the renin-angiotensin system was suggested as the most important factor (Chapman and Gabow 1997).

The renal concentrating capacity test seems to be a valuable indicator for identification of patients with more advanced form of the disease and with an increased risk for elevated ambulatory blood pressure at daytime but also at nighttime.

Our results provide the evidence that the early impairment of renal concentrating capacity should be considered besides PKD1 gene, decreased glomerular filtration rate or advanced cystic kidney degeneration as a further risk factor for the development of arterial hypertension and consequently for the progression of the disease towards chronic renal failure.

In our cohort of children and adolescents, a normal renal concentrating capacity almost excluded arterial hypertension because only one out of 22 patients (5 %) with urine osmolality higher than 900 mOsmol/kg had hypertension detected by ABPM. On the contrary, the decreased concentrating capacity was associated with hypertension in 35 % of children.

In conclusion, renal concentrating capacity is decreased in more than 50 % of children with ADPKD and is linked to ambulatory blood pressure and the number of renal cysts. The decreased concentrating capacity should be considered as an early functional marker of this progressive disease and as a further risk

factor for development of arterial hypertension. We can recommend the renal concentrating capacity test as a routine examination in all pediatric patients with ADPKD because the impairment of tubular function is significantly associated with arterial hypertension, an important and treatable risk factor for progression of this disease towards chronic renal failure.

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