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Original article

Blood pressure and renal function in autosomal dominant polycystic kidney disease

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Abstract. The purpose of this study was to identify hypertension in children and adolescents in an early stage of autosomal dominant polycystic kidney disease (ADPKD) by the application of ambulatory blood pressure monitoring (ABPM) over 24 h; 32 children and adolescents (mean age 12.3 ± 4.7 years) were examined. The diagnosis was based on family history and ultrasound examination. In 21 children ADPKD was confirmed by molecular genetic analysis. At the time of the study, 45% patients were asymptomatic and all had glomerular filtration rates (GFRs) $\geq$65 ml/min per 1.73 m^2. By ABPM, 11 patients (34%) were defined as hypertensive (systolic or diastolic blood pressure $>$95th percentile), including 4 with an exclusive nocturnal hypertension. Of 7 patients with daytime hypertension, 4 had normal blood pressure by casual measurements. The nocturnal dip in blood pressure was reduced in 2 patients. Blood pressure correlated with renal size, but not with GFR, concentrating capacity, proteinuria, and plasma renin activity. The study reveals an early trend for increased blood pressure in children with ADPKD, requiring close supervision.

Key words: Autosomal dominant polycystic kidney disease – Hypertension – Ambulatory blood pressure monitoring – Renal function – Ultrasonography

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder leading to end-stage renal disease (ESRD) [1]. Many studies have demonstrated that signs and symptoms may be observed in the 1st decade of life [2–5]. Rarely, the disease manifests in infancy, presenting with severe complications such as chronic renal failure and hypertension [6, 7]. Family screening by ultrasonography and analysis of genetic markers now allow detection of ADPKD in most gene carriers in the absence of clinical manifestations [7–10]. Although the value of family screening remains controversial [11], carriers of PKD gene mutations might benefit from resulting interventions to improve the prognosis of the disease.

Family screening may be especially useful for identifying hypertension, which is known as an early risk factor for the progression of renal disease in ADPKD and contributes to the high cardiovascular mortality [12–15]. About 60%–75% of adults with ADPKD have increased blood pressure (BP) before renal function is impaired [1, 8, 16]. In children with ADPKD, hypertension seems to be less prevalent, but systematic studies are rare [8, 17, 18]. Recently, ambulatory blood pressure monitoring (ABPM) over 24 h has been introduced as a diagnostic tool to assess BP in children. This method allows more reliable evaluation of BP changes than casual BP recordings [19, 20]. We applied ABPM in the affected offspring of parents with ADPKD, with the aim of identifying hypertensive children and adolescents at an early stage of the disease.

Patients and methods

Parents and patients. Thirty-two children and adolescents (18 boys), originating from 29 parents with ADPKD, were investigated; 25 affected parents (11 males) had a mean age at onset of clinical symptoms of 26.0 ± 7.8 (range 10–43) years; 4 parents were asymptomatic. The diagnosis was based on a positive family history combined with characteristic ultrasound features and/or molecular genetic analysis. At the time of the study, the mean age of the parents was 37.7 ± 7.3 (range 26–58) years; their serum creatinine levels (SCr) were $>$105 μmol/l in 7; 3 parents had entered ESRD.

All children reported here fulfilled the ultrasonographic criteria of ADPKD [21], with 1 exception who had only a single unilateral cyst. Their age at the time of diagnosis was 8.2 ± 4.2 (range 0.2–17.0) years and at the time of ABPM 12.3 ± 4.7 (range 3.4–19.4) years. The diagnosis of ADPKD was supported by molecular genetic analysis with the DNA probe 3′ HVR for PKD-1 in all of the 21 children examined, including the child with a single unilateral cyst.

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Methods. Abdominal ultrasonography was performed using a Toshiba 270 SSA (Japan) instrument. The kidney structure, volume, and length were analyzed and compared with normal standards [22]. Fresh urine specimens were examined for cells, blood, and protein (by dipstick). In addition, urine was collected over a 12- to 24-h period in the majority of patients for quantitative measurement of total protein (Biuret method), albumin (turbidometry), and creatinine. SCr and serum urea were measured and the blood count was done in all patients using standard methods. Glomerular filtration rate (GFR) was estimated from SCr and height [23]. Plasma renin activity (PRA) and erythropoietin were determined by radioimmunoassay. Renal concentrating capacity was evaluated in 14 children by measuring urine osmolality 4 h after nasal application of 5 μg/kg 1-deamino-8-D-arginine-vasopressin (DDAVP Ferring-Léčiva, Czech Republic) [24].

ABPM was performed over 24 h using a SpaceLabs 90207 oscillometric monitor. Each child had a casual measurement of BP immediately prior to ABPM. BP was automatically recorded every 20 min during the daytime and every 30 min at night. One child provided sufficient ABPM data only during the nighttime. In most children, a record of their activity during ABPM was obtained. Mean BP during the daytime and at nighttime were calculated and compared with standards obtained in healthy German children and adolescents of the same sex and height [25]. BP was quantified as standard deviation scores (SDS) from the mean of normal children and correlated for height, according to the following formula: SDS = (X–X50): SD50, where X is the individual′s measurement, X50 the mean in the healthy population, and SD50 the standard deviation of the normal population mean. For the expression of BP as SDS unpublished data from the multicenter study were used (M. Soergel, personal communication). We also calculated the nocturnal dip in BP as a percentage of mean nighttime BP compared with mean daytime BP [25]. Hypertension was defined as a mean systolic *or* diastolic BP during the daytime *or* nighttime exceeding the 95th percentile. No patient was treated with antihypertensive drugs at the time of the study. In 16 patients who remained off such therapy, ABPM was repeated 5–13 months after the first ABPM study.

Statistical analysis. The data were analyzed using Student's t-test for random samples. Correlations between parameters were calculated using the SAS statistical program.

Results

Clinical manifestations

In 18 children and adolescents the following manifestations were noted in the past history at the time of the ABPM study: headache 12, abdominal or flank pain 9, epistaxis 4, enuresis 3, repeated urinary tract infections 3, polyuria/polydipsia 2, fatigue 2, and urolithiasis 1. The remaining 14 children were asymptomatic. There was no significant difference in the presence or absence of symptoms between the offspring inheriting the disease from mothers or fathers.

Ultrasound findings

One or more unilateral cysts were found in 3 children (mean age 4.4, range 3.4–5.7 years), one to five bilateral cysts in 4 children (mean age 7.7, range 4.1–12.4 years), and more than five bilateral cysts in 25 children (mean age 13.8, range 6.4–19.4 years). Mean renal length was + 2.04 SDS (range –2.0 to + 13.0 SDS), being above 2 SDS of normal children in 39% of kidneys. Mean renal volume was + 1.77 SDS (range –2.5 to + 13.0 SDS), being >2 SDS above the mean of normal children in 35% of kidneys. Ultrasonography revealed no cysts in liver, spleen, or pancreas.

Table 1. Standard deviation scores (mean values of SDS ± SD) of ambulatory blood pressure data of children with autosomal dominant polycystic kidney disease compared with German standards [25]

	Mean SDS ± SD Boys (n = 18)	P	Mean SDS ± SD Girls (n = 14)	P
Daytime systolic BP	0.38 ± 0.71	0.0057 (NS)	0.98 ± 0.97	0.006**
Daytime diastolic BP	0.11 ± 0.61	0.245 (NS)	0.66 ± 0.83	0.013*
Nighttime systolic BP	0.74 ± 0.72	0.0019**	0.94 ± 0.97	0.006**
Nighttime diastolic BP	0.86 ± 1.17	0.0019**	0.72 ± 0.86	0.01**
Dip of systolic BP	10.1 ± 4.1%	0.0045**	13.8 ± 2.8%	0.26 (NS)
Dip of diastolic BP	16.2 ± 7.6%	0.0105**	22.9 ± 4.9%	0.77 (NS)

* $P < 0.05$ vs. height- and sex-matched controls
** $P < 0.01$ vs. height- and sex-matched controls

Laboratory findings

Microscopic hematuria was observed in 6 of 32 patients (19%), total proteinuria >100 mg/m^2 per 24 h in 7 of 24 patients (29%), and microalbuminuria >25 mg/l in 11 of 17 patients (64%). In all children, SCr, urea, and blood counts were within age-related normal limits. Mean estimated GFR at the time of ABPM study was 87.0 ± 18.1 (range 65–153) ml/min per 1.73 m^2. Renal concentrating capacity was decreased (urine osmolality <900 mmol/kg) in 8 of 14 children (57%); 5 of the children with low concentrating capacity had a GFR >70 ml/min per 1.73 m^2. PRA was elevated, according to age-related normal values, in 8 of 23 (35%) normotensive and in 3 of 9 (33%) hypertensive patients. Plasma erythropoietin levels were normal (2–16 mU/ml) in all 15 patients examined except 1 (<2 mU/ml).

Blood pressure

By casual BP recordings, systolic BP was >95th percentile in 2 patients and diastolic BP in 3 patients. Table 1 and Figs. 1 and 2 summarize the findings obtained in the first ABPM study, expressed as SDS from the means of control subjects of the same height [25]. In female patients with ADPKD, systolic and diastolic BP were significantly higher than controls both during the daytime and at nighttime. In males, this applied only to BP measured at night. Generally the SDS of BP was higher in female than in male patients (not significant). Sixty-one percent of patients had mean systolic and/or diastolic BP values above the mean of controls during the daytime and 82% at nighttime. Altogether, 11 patients (34%, 5 males, 6 females) had a mean systolic or diastolic value >95th percentile in the first ABPM study; 4 of these had hypertension exclusively

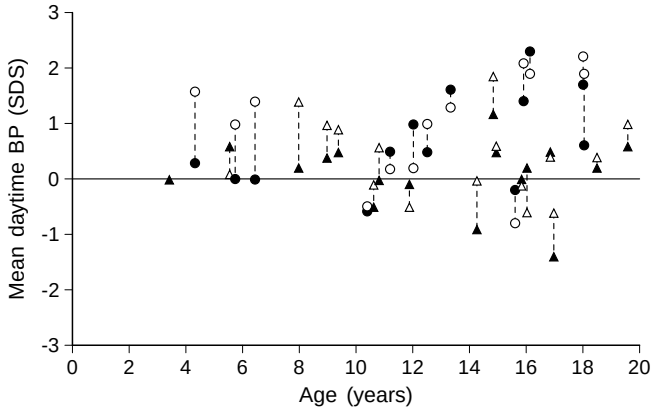

Fig. 1. Mean daytime systolic (*syst*) and diastolic (*diast*) blood pressure [(*BP*), standard deviation score (*SDS*)] in 17 boys and 14 girls with autosomal dominant polycystic kidney disease (ADPKD). Δ, boys syst; ○, girls syst; ▲, boys diast; ●, girls diast

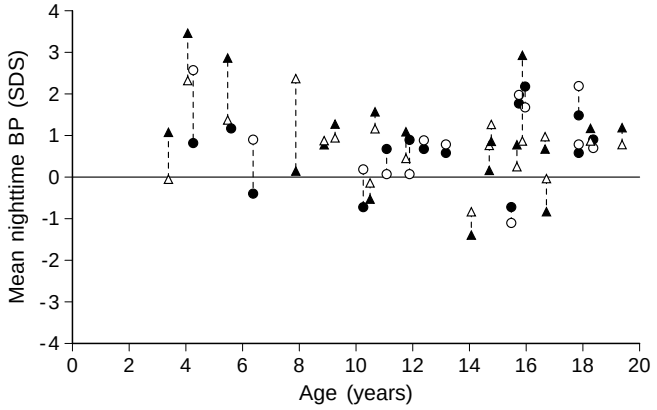

Fig. 2. Mean nighttime systolic and diastolic BP in 18 boys and 14 girls with ADPKD. Δ, boys syst; ○, girls syst; ▲, boys diast; ●, girls diast

during the daytime, 4 at nighttime, and 3 at both times. ABPM detected elevated systolic and/or diastolic daytime values in 4 of 28 patients with normal casual BP values. Conversely, ABPM reclassified 1 of 4 patients as normotensive during the daytime whose casual BP values were in the hypertensive range.

The mean nocturnal dip in BP for both sexes combined was 12% ± 4% (range 3%–18%) for systolic BP and 19% ± 7% (range 1%–31%) for diastolic BP, compared with 13% ± 6% and 23% ± 9% in the normal pediatric population [25]. Only in 1 patient was the nocturnal dip in mean systolic BP reduced below 5%, and in 2 patients the dip in mean diastolic BP was reduced below 11% (corresponding to the 10th percentiles, respectively).

In the 16 patients who underwent repeated ABPM, we noted a slight but insignificant decrease in mean systolic and diastolic BP levels compared with the figures obtained in the first ABPM study.

No significant correlation was found between the ABPM results and total proteinuria, renal concentrating capacity, GFR, and PRA, but there was a significant correlation between mean daytime and nighttime systolic and diastolic SDS and SDS of renal volume ($r = 0.52$, $P = 0.048$) or renal length ($r = 0.86$, $P = 0.0003$), and a borderline correlation between daytime diastolic BP and microalbuminuria ($r = 0.36$, $P = 0.08$). Since this study was performed, antihypertensive drug therapy has been given to 2 children; the other patients await confirmation of hypertension by ABPM.

Discussion

By ultrasonography, more than 90% of presumed carriers of the PKD1 gene mutation can be identified before the age of 20 years [10]. The question arises whether early diagnosis by ultrasonographic screening of the general population [10], urinary mass screening [26], or application of molecular genetic techniques would benefit young individuals with ADPKD. The argument was put forward that early recognition of treatable complications could delay renal deterioration and prolong life expectancy [11].

In the group of children and young adolescents presented here, the diagnosis of ADPKD was derived from family screening by ultrasonography and confirmed in 21 patients by proving linkage to the PKD1 region. Our investigation confirms that ADPKD has a highly variable clinical expression [1, 5]. Almost half of the gene carriers were offspring of adults with symptomatic ADPKD, but had no clinical manifestation at the time of our study. Renal size was increased only in about a third of children. Proteinuria and microscopic hematuria were found in similar proportions as in earlier studies [2, 5, 7, 8]. GFR was within normal limits in all our ADPKD patients, in contrast to some reports in symptomatic ADPKD children [5, 7]. Renal concentrating capacity was reduced in a similar proportion as in a smaller series reported earlier [3].

Hypertension is probably the most important complication besides renal failure in children with ADPKD. Its main pathomechanism appears to be sodium retention and stimulation of the renin-angiotensin system [27, 28]. In our study, high PRA was observed even in the absence of hypertension. Hypertension is important because it causes deterioration of the kidney, brain, and other organs, either by itself or in association with other cardiovascular complications [13]. It is often not recognized in the early stages of the disease [7, 16]. In a recent study, 29% of adult patients with previously unidentified ADPKD were found to have increased BP [9].

In children with ADPKD, hypertension is less common than in adult patients and seems rarely to be an initial symptom [5]. Its prevalence obviously depends on the stage when the disease is detected and the presence of other clinical manifestations. Hypertension becomes more prevalent with deterioration of renal function [14]. With very early and severe clinical presentation hypertension may be a predominant symptom in children with ADPKD [6, 7]. In different series also comprising asymptomatic children and adolescents, the prevalence of hypertension, as assessed by casual recordings, was 25%–30% [4, 5, 8, 17]. In a German multicenter study, 13 of 38 children with ADPKD started antihypertensive drug therapy between the age of 1 month and 16 years [5]. It appears, however, from comparative

studies that hypertension is less prevalent in children with ADPKD than those with the recessive type of PKD [3, 4, 29, 30], in line with the earlier onset and more progressive course of the latter.

In contrast to earlier studies, we failed to observe any significant relationship between hypertension and renal function, probably due to the mild degree of functional impairment. We confirmed, however, the association between BP and renal size described in adult patients with ADPKD [31]. These authors speculated that early initiation of hypertension may relate to bilateral renal ischemia secondary to cyst alteration of the renal vasculature leading to increased kidney size.

Most clinical studies of hypertension in ADPKD have been based only on casual BP recordings. Earlier investigations have shown that casual BP recordings, at least when taken in the office, do not represent the individual average BP level [19, 20]. In addition, they cannot estimate circadian BP variations, which seem to have a prognostic significance with respect to cardiovascular risk [32]. In our study population, we therefore applied ABPM, although we recognize its limitations. We found that a proportion of patients labelled as normotensive by casual BP measurement actually had hypertension when assessed by ABPM. Despite the paucity of clinical symptoms, we found that one-third of the ADPKD children screened by ABPM had a mean systolic and/or diastolic BP above the 95th percentile during the daytime and/or at nighttime, and 82% had mean values above the normal medians. A similar study applying ABPM in a smaller number of affected children from ADPKD families (n = 12) recorded no significant difference between mean arterial BP compared with controls, although a comparable group of patients aged 15–25 years had increased BP during the daytime and nighttime [18]. The reasons for the discrepancy between these and our results might include the younger age of the children (who all were asymptomatic) and the limited size of the control group [18].

Our study revealed that in 4 of the 11 patients defined as hypertensive, mean systolic or diastolic BP exceeded the 95th percentile only at night and not during the daytime. This may be of prognostic interest, because in adults nocturnal hypertension or a reduced nocturnal dipping of BP was more closely associated with increased cardiovascular risk [33] and had a faster progression than daytime hypertension [34]. It should be noted, however, that only a few of our children and adolescents had a reduced dipping, which confirms recent results in adult (normotensive and hypertensive) ADPKD patients in the absence of renal failure [35]. Further studies are needed to confirm these observations in young patients with ADPKD. The increased left ventricular mass found earlier in asymptomatic children and adolescents with ADPKD supports the suspicion that the cardiovascular system is compromised very early in this disease [18].

In conclusion, ABPM revealed that in the absence of renal insufficiency 34% of children and adolescents in an early stage of ADPKD are hypertensive, either during the daytime, at nighttime, or both. Hypertension may be missed if only casual recordings are taken. Regular ABPM is recommended in these patients to allow the early initiation of antihypertensive treatment and to reduce cardiovascular risks in ADPKD.

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Literature abstract

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Prednisone dosage and pregnancy outcome in renal allograft recipients

Jacob Bar, Benjamin Fisch, Clara Wittenberg, Ilana Gelerenter, Geoffry Boner, and Moshe Hod

Background. The literature contains reports of 2309 pregnancies in some 1600 women who have undergone renal transplantation. Certain pre-pregnancy factors, especially hypertension, renal graft dysfunction, short interval between transplant and pregnancy, and high immunosuppressive drug dosage, appear to increase the neonatal risks.
Method. We describe the outcome of 42 pregnancies in 27 allograft recipients at Rabin Medical Center (Beilinson Campus) in Israel during the last 8 years. All were treated with combination immunosuppression regimens.
Results. The average interval from transplantation to conception was 3.7 ± 0.4 years (2 months to 9 years). Rejection episodes occurred in 37% prior to pregnancy but in none during or immediately after pregnancy. Twenty-eight percent of the pregnancies ended in therapeutic or spontaneous abortions, and 29 of the 30 deliveries ended in a live birth. The prematurity rate (63%) was similar to that described in the literature for this patient group. Renal deterioration was evident in seven women (26%) within 2 years after delivery. Use of 7.5 mg/d prednisone (vs. 10 mg/d) before pregnancy was observed as the most significant preconception parameter related to better pregnancy outcome. A long interval from transplantation to conception and lack of pre-existing hypertension were also significant.
Conclusion. The better pregnancy outcome associated with lower prednisone dosage is probably related to the fact that the patients selected to receive the low-dose regimen have had a longer and less complicated post-transplantation course.