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Grayscale ultrasound characteristics of autosomal dominant polycystic kidney disease severity – an adult and pediatric cohort study

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Abstract

Introduction: The most common hereditary kidney condition is autosomal dominant polycystic kidney disease. It is the cause of 5–10% of end-stage renal disease. Its symptoms are generally late-onset, typically leading to development of hypertension and chronic kidney disease. Ultrasonography is the imaging modality of choice in its diagnosis and management. The aim of this study is to determine the diagnostic value of grayscale ultrasound imaging in evaluating disease severity. **Materials and methods:** The study group consisted of 81 patients diagnosed with autosomal dominant polycystic kidney disease, 35 adults and 46 children. Inclusion criterion for adults was the presence of at least 10 large cysts in each kidney; children included into the study had developed at least 1 large renal cyst in each kidney. The number of large cysts, echogenicity of kidney parenchyma, cortical thickness and presentation of cortex/medulla boundary were assessed with the use of Logiq E9 apparatus (GE Healthcare, Netherlands). Patients were divided into groups, based on these morphological parameters. Kidney function was assessed according to serum creatinine concentration and creatinine clearance. Statistical analysis was performed, with p-value lower than 0.05 considered as significant. **Results:** The number of cysts and the degree of parenchymal dysfunction were the determinants of creatinine level and creatinine clearance, with the second predictor proving stronger. **Conclusions:** We recommend that an ultrasound kidney examination in patients with polycystic kidney disease should include evaluating renal parenchyma and the number of cysts for better assessment of disease severity.

Introduction

Renal cysts are the most common kidney lesion in adults, found in up to 50% of people aged over 50 years. They may be hereditary, developmental or acquired, and are most often incidentally diagnosed with ultrasonography (US). Benign, so-called "simple cysts" on ultrasound appear as anechoic, thin-walled lesions with well-defined margins and lacking calcifications or septa. Cysts deviating from this appearance warrant further examination to exclude other, potentially malignant lesions.

The most common hereditary kidney disease is autosomal dominant polycystic kidney disease (ADPKD), affecting 1:400 – 1:1000 individuals worldwide and the cause of 5–10% of end-stage renal disease (ESRD) in developed countries[1]. Its symptoms are generally late-onset and manifested by focal development and progressive enlargement of renal cysts, typically leading to development of hypertension and chronic kidney disease (CKD) by late-middle age. Other organs may be affected as well, resulting in extrarenal cysts in the liver and pancreas, vascular abnormalities, cardiac valvular defects and abdominal wall hernias.

Ultrasonography is the imaging modality of choice in ADPKD, due to its accessibility, low cost and lack of ionizing radiation. Sonographic criteria established for ADPKD diagnosis, based on patient age, number of renal cysts and family history, show high positive predictive value and sensitivity[2]. Ultrasound imaging can also provide important information for evaluating disease progression.

We focused on grayscale US features such as increased parenchymal echogenicity, reduction of cortical thickness, irregular kidney margins and loss of the cortex/medulla boundary, all found in patients with advanced ADPKD.

Our aim was to determine the diagnostic value of grayscale ultrasound imaging in evaluating ADPKD severity.

Materials and methods

81 patients diagnosed with ADPKD were recruited from the Pediatric and General Nephrology Outpatient Clinics. The group was comprised of 51 females and 30 males. Both gender groups of patients were of similar age (24.6 ± 15.5 vs. 21.9 ± 11.3 years for females and males, respectively). 35 participants were adults with multiple, large renal cysts in both kidneys. The remaining 46 patients were children of the aforementioned adults, aged 1 to 17 years, who developed multiple renal cysts discernable in US imaging.

Inclusion criterion for adults was the presence of at least 10 large cysts in each kidney (≥ 10 mm in diameter); children included into the study had developed at least 1 large renal cyst (≥ 10 mm in diameter) in each kidney.

Abdominal US examination was performed for kidney evaluation with Logiq E9 apparatus (GE Healthcare, Netherlands). The following parameters were assessed: the number of large cysts (≥10 mm in diameter), echogenicity of kidney parenchyma, cortical thickness (measured in the coronal plane over a medullary pyramid) and presentation of cortex/medulla boundary.

Increased parenchymal echogenicity is one of the sonographic findings in patients with ADPKD, as shown in Fig. 1 and Fig. 2. It may be the result of the presence of microcysts below the threshold of resolution, vascular reflexes, or parenchymal dysfunction due to pressure-related ischemia[3,4]. It is an important marker of CKD advancement, evaluated by comparing the echogenicity of the renal cortex, medulla and pyelic sinus with the parenchyma of the liver or spleen. Standard echogenicity grading ranges from 0 (renal cortex is hypoechoic vs. liver) to III (echogenicity

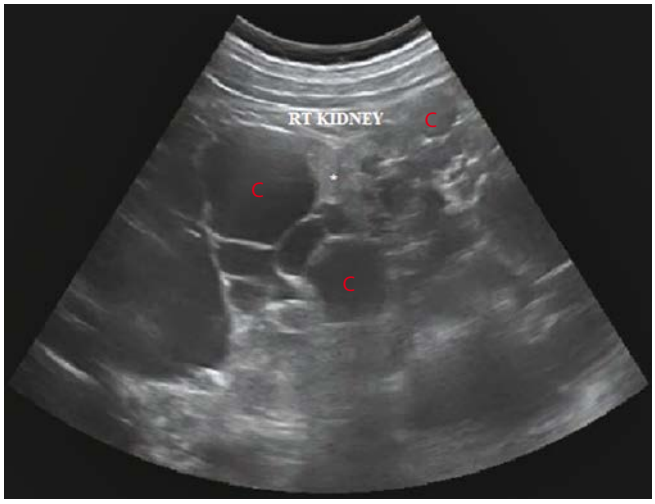

Fig. 1. *Multiple kidney cysts (c) in a patient with ADPKD, renal parenchyma (asterisk) has increased echogenicity, corticomedullary differentiation is not discernible*

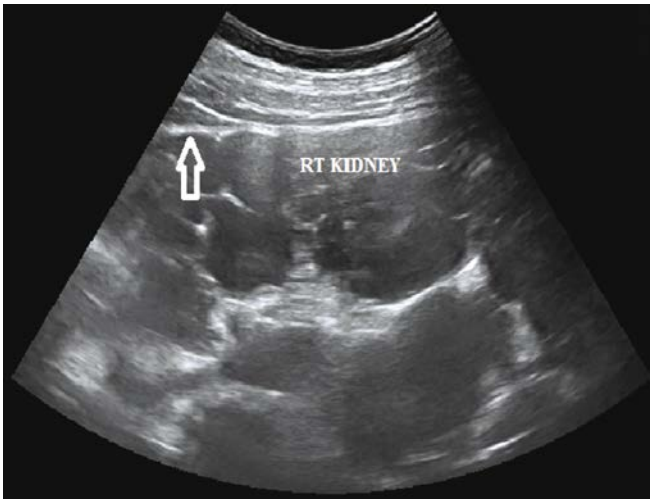

Fig. 2. *Grayscale ultrasound image of a kidney (in the coronal plane) in patient with ADPKD, white arrow shows a hyperechoic, thin layer of the renal cortex*

Parameters		Right kidney (n = 81)	Left kidney (n = 81)	P value
Number of cysts [n (%)]	<10	22 (27.16)	22 (27.16)	0.9810
	10–20	20 (24.69)	19 (23.46)	
	>20	39 (48.15)	40 (49.38)	
Degree of parenchymal dysfunction [n (%)]	0	34 (41.98)	31 (38.27)	0.8798
	1	19 (23.46)	21 (25.93)	
	2	28 (34.57)	29 (35.80)	
Parenchyma thickness [mm; median (IQR)]		13 (8–16)	13 (10–16)	0.8352
IQR – interquartile range				

Tab. 1. *Comparison of ultrasound characteristics between two kidneys*

of renal parenchyma same as pyelic sinus). This grading, however, does not include other changes in parenchymal presentation in ADPKD, potentially reflecting kidney dysfunction.

As all aforementioned morphological parameters change simultaneously with advancement of ADPKD, we divided patients into three groups based on the presentation of renal parenchyma:

- group 0 – renal parenchyma is equally echogenic or mildly hyperechoic compared to the liver or spleen, preserved cortical thickness and corticomedullary differentiation
- group I – a moderate increase in the echogenicity of renal parenchyma, moderate reduction of cortical thickness (8–15 mm)
- group II – severe cortical thickness reduction (< 8 mm), loss of corticomedullary differentiation.

Furthermore, regardless of parenchymal presentation, all patients have been divided into three groups, depending on the total number of large cysts in both kidneys – less than 10 cysts, between 10 and 20 cysts, and over 20 cysts respectively. Criterion of 20 cysts was applied as the upper limit, because differentiation of more than 20 large lesions in one organ would be unreliable.

Evaluation of kidney function was assessed by measuring the serum creatinine concentration (in mg/dL) and creatinine clearance (mL/min/1.73 m^2). The latter was calculated using the Cockcroft-Gault formula for adults and "Bedside Schwartz" formula for children.

All participants aged 16 year old or more and guardians of individuals younger than 16 years old signed an informed consent form for participation in the research. The study protocol was approved by the local bioethical committee (Instytut Centrum Zdrowia Matki Polki, Łódź, Poland, protocol number: 67/2015).

The statistical analysis was performed using Statistica 12 software (StatSoft Polska, Cracow, Poland). A p-value lower than 0.05 was considered significant.

Parameters		Degree of parenchymal dysfunction [n (%)]		
		0	1	2
Number of cysts (≥10 mm in diameter)	<10	42 (64.62)	2 (5.00)	0 (0.00)
	10–20	9 (13.85)	23 (57.50)	7 (12.28)
	>20	14 (21.54)	15 (37.50)	50 (87.72)

Tab. 2. *Distribution of parenchymal dysfunction between patients with different numbers of large cysts*

The Chi^2 test was used for comparisons of nominal data. The normality of the continuous data distribution was checked with the Shapiro-Wilk test. Due to distribution other than normal comparisons of continuous variables between two kidneys and two different groups were performed with the Wilcoxon signed rank test and the Mann-Whitney test, respectively. Differences in continuous variables among three groups were assessed with Kruskal-Wallis ANOVA with dedicated post-hoc tests. Multiple linear regression analysis was applied to evaluate factors affecting metabolic markers of kidney function.

Results

There were no differences between the right and the left kidney in the number of cysts, sonographic signs of parenchymal dysfunction or parenchymal thickness, as shown in Tab. 1. Thus, pooled data from both kidneys were used for further calculations. The association between parenchymal dysfunction and the number of cysts has been presented in Tab. 2.

According to analysis of variance, creatinine levels and creatinine clearance differed significantly among patients with different degrees of parenchymal dysfunction (p < 0.001 for both parameters). The results of post-hoc tests have been presented in Tab. 3 and in Fig. 3.

In regression analysis both the number of cysts and the degree of parenchymal dysfunction were significant deter-

Degree of parenchymal dysfunction		0	1	2
Creatinine level [mg/d] (median and IQR)		0.86 (0.76–0.92)	1.3 (1.07–1.39)	1.51 (1.33–2.34)
0	0.86 (0.76–0.92)	–	0.0002	0.0001
1	1.3 (1.07–1.39)	0.0002	–	0.0003
2	1.51 (1.33–2.34)	0.0001	0.0003	–
Creatinine clearance [mL/min/1.73 m^2] (median and IQR)		88.3 (65.0–97.0)	70.0 (50.0–86.0)	48.0 (35.0–59.0)
0	88.3 (65.0–97.0)	–	0.0023	0.0001
1	70.0 (50.0–86.0)	0.0023	–	0.0003
2	48.0 (35.0–59.0)	0.0001	0.0003	–

Tab. 3. *Results of post-hoc tests for evaluation of the differences in creatinine level and creatinine clearance among patients with 3 degrees of parenchymal dysfunction*

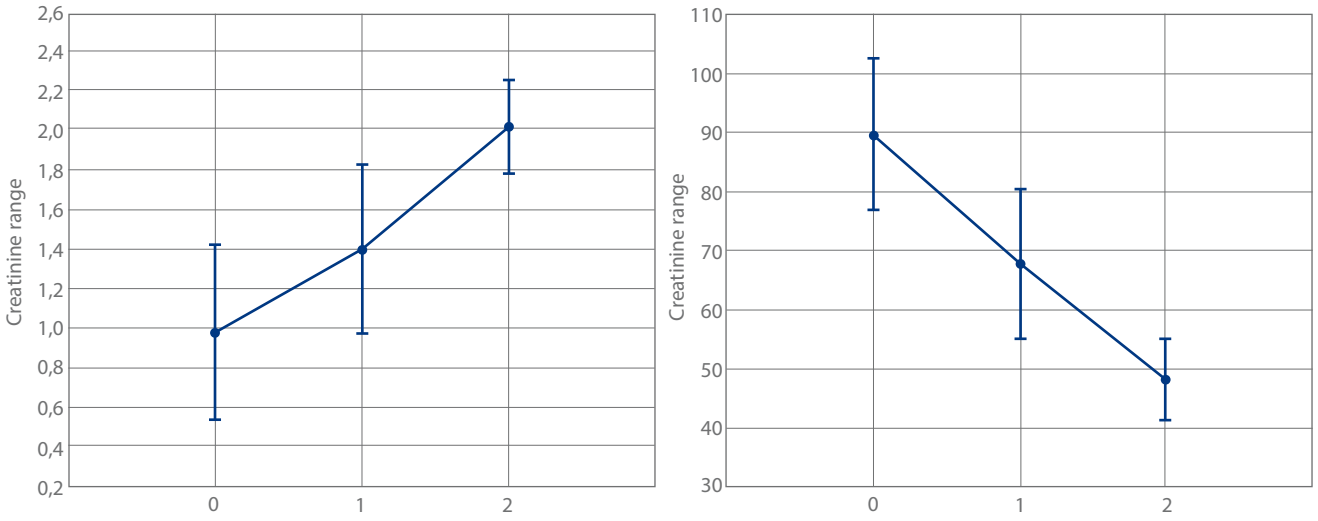

Fig. 3. *Correlations between kidney function and sonographic signs of parenchymal dysfunction*

minants of the creatinine level and creatinine clearance, with the second predictor proving stronger as shown in Tab. 4 and in Fig. 4.

Discussion

Our study has shown that for creatinine clearance the B value for the number of cysts was positive. This is confusing as it might suggest that with increasing number of cysts the clearance improves. However, analysis of variance showed that creatinine clearance varied significantly between the groups of patients with different numbers of large cysts, and it was due to increased clearance in patients with 10–20 cysts compared to patients with more than 20 cysts. This discrepancy may be the result of the relatively small number of patients with 10–20 kidney cysts (less than 20% of the study group). Most children were diagnosed with less than 10 kidney cysts, in the majority of adults more than 20 kidney cysts were found.

ADPKD is caused by *PKD1* and *PKD2* gene mutations (accounting for 85% and 15% of cases respectively). De novo mutations are considered rare, however ADPKD cannot be excluded from the differential diagnosis in people with negative family history who develop renal cysts[5]. Regardless of the genetic form of the disorder sonographic renal manifestations are the same in both groups of patients, with differences in the severity of the disease as patients with *PKD1* pathogenic variant developing cysts earlier than *PKD2* patients. The rate of cystic growth remains the same in both groups[6].

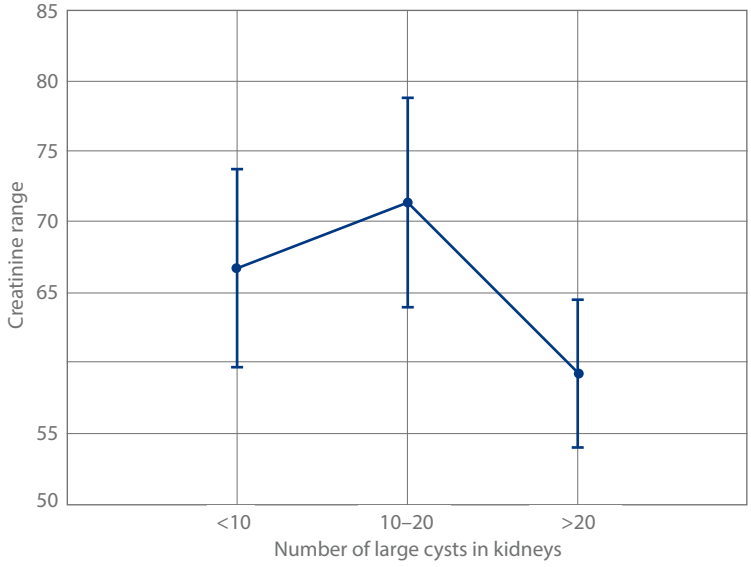

Fig. 4. *Correlations between kidney function and the number of large cystic lesions in the kidneys*

Parameter	Creatinine level		Creatinine clearance	
	B	*P* value	B	*P* value
Number of cysts	0,1663	0,0311	6,1849	0,0256
Degree of parenchymal dysfunction	0,4078	0,0000	–15,2521	0,0000
R^2	0,3604		0,1790	
B – regression coefficient; R^2 – coefficient of determination				

Tab. 4. *Analysis of regression for kidney function parameters*

Most patients with ADPKD have preserved renal function until the fourth or fifth decade of life. Once first signs of renal failure are observed, the majority of patients will reach ESRD within 10 years[7]. Prediction of rapid CKD progression in these patients is critical for averting the possible complications.

While most studies regarding US evaluation of ADPKD include solely patients with renal cysts within the adolescent-adult age range groups, we decided to include children of all ages for better understanding of sonographic kidney presentation and evaluation of future renal function.

Ultrasound imaging plays an important role in both the diagnosis and assessment of ADPKD severity[8]. Cystic growth leads to intrarenal ischemia which activates the renin-angiotensin-aldosterone system[9], in turn stimulating cyst expansion, increasing systemic vascular resistance and sodium retention. This leads to development of renal fibrosis, renal function deterioration and potentially ESRD[10].

Kidney length and height-adjusted total kidney volume (htTKV) have been reported to predict CKD development in patients with ADPKD. Studies carried out by the Consortium for Radiologic Imaging in Polycystic Kidney Disease suggest that individuals with htTKV >600 cc/m will develop CKD stage 3 over a course of 8 years[11]. Bhutani *et al*. found that kidney length over 16.5cm may be used as substitute in such prediction[12]. The fact that these parameters are measurable in grayscale US and the advantages of ultrasonography mentioned earlier further strengthen its role in disease prognosis and patient management.

It should be noted that sonographic measurements are largely operator-dependent. Discrepancies between data obtained in US and magnetic resonance imaging have been shown in previous studies[13,14]. Evaluation of gross kidney morphology in US is easier, and can be performed by medical personnel trained and certified in renal ultrasonography[15].

Distinguishing ADPKD from cysts acquired as a result of primary renal disease can sometimes be problematic, especially in patients with either isolated or numerous lesions. US renal presentation differs in patients with ADPKD from those with acquired renal cysts of different origin. However since these traits may be difficult to evaluate in patients with multiple cysts, a careful and thorough examination is always necessary to obtain maximal information of diagnostic value[16].

As evidenced by our study, there is a positive correlation between deteriorating kidney function (measured by an increase in serum creatinine levels and decrease in creatinine clearance) and the sonographic signs of parenchymal dysfunction, including increase in echogenicity of renal parenchyma, decrease in cortical thickness and loss of corticomedullary differentiation. Similar results were obtained by Siddappa et al. in a study group of patients over 30 years of age[17].

Conclusions

We recommend that a US kidney examination in patients with ADPKD should consist of evaluating not only kidney size but also the signs of renal parenchyma dysfunction and the total number of cysts as they are a reliable source of information in evaluating the advancement of the disease.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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