Original Paper

Sonographic Image of Solitary Kidney in Wilms Tumour Survivors

Mateusz Kosiak^a Joanna Stefanowicz^b Elżbieta Adamkiewicz-Drożyńska^b
Anna Balcerska^b Andrzej Kurylak^c Ewa Demidowicz^d

^aDepartment of Family Medicine. Medical University of Gdansk, Gdansk, ^bDepartment of Paediatrics, Haematology and Oncology. Medical University of Gdansk, Gdansk, ^cPaediatric Nursing Centre.

Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Torun,

^dDepartment of Paediatrics, Haematology and Oncology. Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Torun, Poland

Key Words

Wilms tumour • Survivors • Solitary kidney • Sonography • Renal function • Chronic kidney disease

Abstract

Background/Aims: This study presents an analysis of the sonographic and laboratory parameters of solitary kidney in Wilms tumour survivors (TWs) and compares these parameters with those of healthy individuals. **Methods:** Fifty-three TWs who completed treatment for Wilms tumour and 44 healthy individuals were enrolled. The study protocol consisted of completing a medical history, sonographic examination of the solitary kidney, estimation of glomerular filtration rate (eGFR) by the Schwartz or MDRD formulas, albumin urine excretion and BP measurement. **Results:** Sonographic signs of kidney damage were observed in 22 (41,5%) TWs. The most frequently detected abnormalities are hyperechoic rings around renal pyramids (28,3% TWs). Hypertrophy of the solitary kidney occurred in 71,7% of cases. The mean volume of the solitary kidney was 77% of the sum of the two kidney volumes in the control group. The median eGFR in the TWs group was 117 with 25Q-105,5, 75Q-130 ml/min/1,73 m² vs 131,8 with 25Q-124, 75Q-140 ml/min/1,73 m² in the control group (p=0,000). Six TWs (11,3%) had a value of eGFR below 90 ml/min/1,73 m². Increased urine albumin excretion (> 30 mg/g) was observed in 7 TWs (13,2%) and in 3 (6,8%) individuals in the control group. **Conclusion:** Ultrasonographic abnormalities in solitary kidney of TWs are frequent. The most frequently detected abnormalities are hyperechoic rings around renal pyramids. Sonographic examination of TWs ought to be performed not only to detect tumour recurrence but also to assess the signs of kidney damage and their progression.

© 2018 The Author(s)
Published by S. Karger AG, Basel

M. Kosiak and J. Stefanowicz contributed equally to this work.

Joanna Stefanowicz, MD, PhD

Department of Paediatrics, Haematology and Oncology, Medical University of Gdansk,
7 Debinki Street, 80-952 Gdansk (Poland)
Tel. +48 58 349 28 80, Fax +48 58 349 28 47, E-Mail jstefanowicz@gumed.edu.pl

Introduction

Wilms tumour (TW) is the most common neoplasm of kidney in children [1, 2]. The results of treatment of TW have improved in recent years, reaching 4-year overall survival in the favourable histology group of nearly 90%. The number of children who complete the treatment and survive is increasing [2]. According to the International Society of Paediatric Oncology (*Societe Internationale D'Oncologie Pediatrique* - SIOP), ultrasound examination ought to be performed five to eight times during first five years after treatment in single kidney disease without metastases [3]. The early detection of tumour recurrence or metachronous nephroblastoma in the solitary kidney is the main purpose for this examination [4]. In addition, ultrasound examination provides an opportunity to assess the signs of kidney damage. The signs of kidney damage in ultrasound examination are among the diagnostic criteria for chronic kidney disease (CKD) [5]. According to the National Kidney Foundation (NKF), CKD is defined as either kidney damage or estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m² for more than 3 months [5]. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or in imaging studies [5, 6]. The Kidney Disease, Improving Global Outcomes (KDIGO) recommendations from 2012 define CKD as abnormalities of kidney structure or function, present for > 3 months with implications for health [6]. Signs of kidney damage may indicate the risk of deterioration of kidney function in the future [5]. Wilms tumour survivors (TWs) are at risk of deteriorating renal function and CKD because of the following: decreased number of nephrons after nephrectomy, nephrotoxic side effects of chemotherapeutic agents (carboplatin, cisplatin, ifosfamide, cyclophosphamide) or radiation therapy if the solitary kidney was in the field of radiation [7, 8].

The function of the solitary kidney in TWs has been analysed in several studies. Some of those studies focused on hypertrophy of the solitary kidney [9, 10, 11, 12, 13, 14]. A few recent publications provided insight into the sonographic features of the kidney, underlining the need for detailed analysis [15, 16]. To date, sonographic images of the solitary kidney in prospective studies with control groups have not yet been reported.

The aim of this study was to present the characteristics of sonographic images of solitary kidney in TWs and to compare those characteristics with those of healthy individuals. The second aim of the study was to assess renal function based on estimated glomerular filtration rate (eGFR), urine albumin excretion and urine sediment analysis.

Materials and Methods

This was a cross-sectional prospective study with a control group of healthy individuals.

Patients

Fifty-three individuals (27 females and 26 males) who had undergone nephrectomy and treatment for TW in the Department of Paediatrics, Haematology and Oncology at the Medical University of Gdansk or in the Department of Paediatrics, Haematology and Oncology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, were enrolled.

Patients were excluded from the study if they had one of the following: heminephrectomy on medical history, bilateral TW, congenital abnormality of the solitary kidney or the urinary tract, urinary tract infection at the time of study, tumour recurrence or secondary neoplasm.

Forty-four healthy individuals (20 females and 24 males) were enrolled as the control group. They did not significantly differ from the TW group in terms of age, height, BMI (body mass index) and gender distribution. Individuals were excluded from the group if they had one of the following: medical record of any kidney disease, congenital abnormality of the solitary kidney or urinary tract or infectious disease at the time of the study. A comparison of the TWs and control groups is presented in Table 1.

Methods

The study protocol consisted of completing a medical history, physical examination, sonographic evaluation of the solitary kidney, laboratory tests and blood pressure assessment.

Ultrasound examination

All ultrasound examinations were performed by the same person (M.K.) in the Department of Paediatric & Adolescent Nephrology & Hypertension Medical University

of Gdansk, Poland; in the Department of Paediatrics, Haematology and Oncology, Medical University of Gdansk, Poland; or in the Department of Paediatrics, Haematology and Oncology Ludwik Rydygier Collegium Medicum in Bydgoszcz. Nicolaus Copernicus University in Torun.

The following equipment was used: GE Logiq 500, GE Logiq E and GE Logiq 7 (GE Medical Systems, Waukesha, WI, USA) with convex 3, 5-5, 0 MHz and linear 8, 0-12, 0 probes.

Kidneys were examined in the prone position. Lumbar muscles were used as acoustic windows. The examination conditions were the same for every patient. All patients were asked not to drink any fluids one hour before the examination.

The following sonographic image features were considered: medullo-cortex differentiation, increased echogenicity of renal cortex, scars, hyperechoic rings around pyramids, cysts and calculi.

All individuals had the following parameters of the solitary kidney measured: length, width, depth, volume and parenchymal thickness of the kidney, and length and width of the central echo of the kidney. For the purposes of this study, length of kidney was reported as the percentage of expected length of the normal kidney. This was defined as the kidney length on sonographic examination as a percentage of the hypothetical kidney length that the child would be expected to have if he or she had not undergone nephrectomy. Values of the hypothetical, expected length of kidney were based on Chen et al. using an internet calculator - Mr. Nomogram [17, 18]. Based on obtained data, the following indices were calculated: kidney length/height; parenchymal thickness/kidney length; and length of central echo/length of kidney.

Blood flow in each kidney was assessed using spectral Doppler and colour Doppler options. The resistance index (RI) was evaluated for every patient: $RI = (V_{max} - V_{min}) / V_{max}$. In each measurement, the value of the insonation angle was under 60.

Laboratory tests

All laboratory tests were performed in the Central Laboratory of the Medical University of Gdansk.

Creatinine serum concentrations were assessed using the colorimetric-modified Jaffe method (mg/dL) (Architect c8000).

eGFR in individuals under 18 years of age was estimated with the Schwartz formula: $eGFR [ml/min/1.73 m^2] = k \times height [cm] / serum \ creatinine \ concentration [mg/dL]$, where the constant k was defined using published literature values: $k=0.55$ for children aged 2-12 or adolescent females, and $k=0.7$ for adolescent males [19]. In individuals over 18 years of age, GFR was estimated with the MDRD formula: $eGFR [ml/min/1.73 m^2] = 170 \times (serum \ creatinine \ concentration [mg/dL])^{-0.726} \times (serum \ concentration \ of \ blood \ urea \ nitrogen [mg/dL])^{-0.720} \times (albumin \ serum \ concentration [g/dL])^{0.318} \times 0.762$ (for women) $\times 1.180$ (for African Americans) [20].

Albumin urine excretion was measured in urine spot samples using the immunologic method, Multigent, from Abbott Laboratories (Wesbaden, Germany). Increased excretion of albumin with urine was defined as a urine albumin to creatinine ratio (ACR) of over 30 mg/g [21].

Table 1. Comparison of TWs group and control group. TWs- Wilms tumour survivors. *For variables with a normal distribution, the mean and standard deviation were presented. ** For variables without a normal distribution the median, 25Q, 75Q were presented

Parameter	TWs group n=53	Control group n=44	p
age [years]	12,6±5,6*	11,3±4,9*	0,245
height [cm]	149,2±22,1*	146,5±26,9*	0,588
weight [kg]	42,5±17,7*	44,1±20*	0,685
Sex [F/M]	27/26	20/24	0,590
age at time of diagnosis [years]	2,9 (1,7÷4,3)**	-	-
time from the end of treatment [years]	8,5±5,7*	-	-

Blood pressure

Blood pressure was assessed in all individuals in the TWs and control groups with the Dinamap DPC 120 X-EN GE. Each individual had blood pressure measured three times according to the guidelines of *The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents* [22].

Statistical analysis

Statistical analysis was performed using Statistica 8.0 PL software (Polish version; StatSoft, Tulsa, OK, USA). A normal distribution of the data was verified using the Shapiro-Wilk W-test. Statistical significance between different groups was calculated by one-way analysis of variance (ANOVA), alternatively using the U Mann-Whitney test when the variances in groups were not homogeneous (the homogeneity of variance was determined by the Levene test). Statistical significance between frequencies was calculated by the chi-square test with Yate's correction or Fisher exact test. A correlation analysis was performed using Spearman's methods. The level of significance was set at $p < 0,05$.

Ethics Approval

This study was approved by the Independent Bioethical Committee of Scientific Researchers at the Medical University of Gdansk. Written informed consent was obtained from the legal guardians of the children.

Results

Signs of kidney damage on USG

Signs of kidney damage on sonographic examination in the TW group were observed in 22 individuals (41, 5%). These findings are presented in Table 2. The most frequently detected abnormalities were hyperechoic rings around renal pyramids (Fig. 1). Six TWs (11, 3%) had two abnormalities on sonographic examination. None of individuals in the TWs group had three or more abnormalities.

Hypertrophy of solitary kidney was defined when length of kidney exceeded over value of 95th centile according to height, gender and race. The length of the solitary kidney in thirty-eight (71, 7%) TWs exceeded the value of the 95th percentile, according to height, gender and race.

Mean volume of kidney in TWs group was 77% of a mean sum of two kidneys volume in the control group ($p=0,0034$). A comparison of the sonographic measurements between the TWs and control groups is presented in Table 3.

No differences were observed between the groups in terms of the side of the kidney.

There were correlations in the TWs group between the percent of expected renal length and the following parameters: age ($p=0,0006$) and height ($p=0,0022$).

There were no correlations in the TWs group between percent of expected renal length and following parameters: age at time of diagnosis, time from nephrectomy, and eGFR ($p>0,05$).

There was no significant difference between the TWs and control groups in terms of RI, $p=0,93$. The mean values of RI over 0,65 were detected in seven TWs and in one person in the control group. None of the individuals had mean values of RI over 0,7.

In 22 TWs with abnormalities

Table 2. Abnormalities in sonographic examination In TWs and control group. TWs – Wilms tumour survivors

Signs of kidney damage in sonographic examination	TWs group number of individuals	Control group number of individuals	p
hyperechoic rings around renal pyramids	15	4	0,034*
increased echogenicity of renal cortex	6	0	0,030*
scars	4	0	0,124
calculi	3	0	0,249
cysts	1	0	0,999
diffused medullo-cortex differentiation	0	0	-

on sonographic examination, five also had abnormalities in laboratory tests: in three cases, there was decreased eGFR below 90 ml/min/1, 73 m² without increased albumin excretion; in one person, there was decreased eGFR below 90 ml/min/1, 73 m² with increased albumin excretion (ACR >30 mg/g); and in one person, there was increased albumin excretion (ACR > 30 mg/g) with normal eGFR.

eGFR

Mean eGFR was statistically lower in the TWs than in the control group: 117 (25Q-106; 75Q-130) ml/min/1, 73 m² vs 131, 8 (25Q-124; 75Q-140) ml/min/1, 73 m² (p=0, 000). Six TWs (11, 3%) had values of eGFR below 90 ml/min/1, 73 m². None of the individuals in the control group had decreased eGFR below 90 ml/min/1, 73 m².

Urine albumin excretion

Increased urine albumin excretion (ACR > 30 mg/g) was observed in 7 TWs (13, 2%) and in 3 (6, 8%) individuals in the control group. There was no significant difference in terms of mean ACR between the groups (p=0, 37). In two of these seven TWs, other abnormalities were also observed: one person had decreased eGFR (88, 4 ml/min/1, 73 m²) and signs of kidney damage on USG (hyperechoic rings around renal pyramids, calculi); one person had increased creatinine concentration (0, 91 mg/dl) and signs of kidney damage on USG (hyperechoic rings around renal pyramids, increased cortex echogenicity); and in the other five TWs, there were no abnormalities in laboratory tests or on sonographic examination, although one of the five TWs had mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) over the 95th percentile, and one TWs had SBP over the 95th percentile.

Urinalysis with urine sediment assessment

We observed no abnormalities in the urine sediments.

Fig. 1. Hyperechoic rings around renal pyramids.

Table 3. Comparison of sonographic measurements between TWs group and control group. TWs– Wilms tumour survivors. LK– left kidney; RK – right kidney; p – level of significance; RI – resistance index; *For variables with a normal distribution, the mean and standard deviation were presented. ** For variables without a normal distribution the median, 25Q, 75Q were presented

Parameter	Side	TWs group LK n=22 RK n=31	Control group n=44	p
length of kidney [mm]	left	112 (96÷124)**	98 (84÷105)**	0,0010
	right	116±14,8*	93,8±14,0*	0,0000
% expected renal length	left	115,2 (111,1÷122,5)**	101,8 (81,4÷108,3)*	0,0000
	right	122,5 (116,8÷127,6)**	98,3 (94÷102,6)**	0,0000
volume of kidney [ml]	left	138,6 (78,9÷182,2)**	88,2 (62,5÷110,6)**	0,0026
	right	129,4 (106,2÷180,6)**	90,6 (58,7÷112,6)**	0,0002
parenchyma thickness [mm]	left	12,9 ±2,8*	13,6±2,2*	0,3210
	right	14,3±2,9*	13,7±2,0*	0,2900
length of central echo [mm]	left	79,1±11,7*	69,4±11,6*	0,0027
	right	80,6±12,7*	67,2±14,9*	0,0002
length of kidney / height	left	0,076±0,008*	0,066±0,006*	0,0002
	right	0,077±0,007*	0,065±0,005*	0,0000
parenchyma thickness / length of kidney	left	0,12 (0,1÷0,12)**	0,09 (0,09÷0,1)**	0,0000
	right	0,11 (0,09÷0,12)**	0,09 (0,09÷0,1)**	0,0070
length of central echo / length of kidney	left	0,698 (0,686÷0,716)**	0,733 (0,701÷0,755)**	0,04470
	right	0,696 (0,662÷0,0727)**	0,728 (0,703÷0,764)**	0,0039
RI		0,58 (0,55÷0,63)**	0,59 (0,57÷0,61)	0,93

Renal injury and Chronic Kidney Disease

CKD in TWs might be a consequence of nephrectomy. Six TWs (11, 3%) had eGFR of 60–89 ml/min/1.73 m². These individuals could be classified as G2 category if confirmed after three months.

Of the patients with eGFR ≥ 90 ml/min/1.73 m², no abnormalities (neither on sonographic examination nor in laboratory tests) were found in 26 TWs, while 21 TWs had sonographic or laboratory signs of kidney damage. Fifteen of these twenty-one TWs had abnormalities on sonographic examination: in eight cases, hyperechoic rings around renal pyramids were the only abnormalities diagnosed. None of these TWs underwent potentially nephrotoxic chemotherapy or irradiation. Five out of twenty-one TWs had increased albumin excretion with no signs of kidney damage on ultrasound examination. One TWs had increased albumin excretion (ACR – 148, 9 mg/dl) and abnormalities on sonographic examination (increased cortex echogenicity, hyperechoic rings around renal pyramids).

Five out of six TWs at risk for stage II of CKD had signs of kidney damage on ultrasound examination. One of those five individuals also had increased albumin excretion. One out of six TWs at risk for stage II of CKD had decreased eGFR (60–89 ml/min/1.73 m²) with no abnormality on sonographic examination and with no increased albumin secretion.

Blood Pressure

In the TWs group, mean SBP >95th percentile and DBP >95th percentile were in seven individuals (13, 2%). Another five individuals (9, 4%) had values of mean SBP over the 95th percentile. In one case (1, 9%), the mean values of SBP and DBP were between the 90th and 95th percentiles. None of the individuals in the control group had arterial hypertension. Ten individuals (22, 7%) in the control group had mean values of SBP and DBP between the 90th and 95th percentiles.

The treatment of TW was performed according to the following protocols: SIOP 9–4 individuals; SIOP 1993–30 individuals; and SIOP 2001–19 individuals. Eight TWs were treated with potentially nephrotoxic chemotherapeutic agents (carboplatin, cisplatin, ifosfamide, cyclophosphamide). There were no significant differences in terms of sonographic parameters or eGFR between TWs who received and did not receive potentially nephrotoxic chemotherapeutic agents. Those two groups did not differ in terms of age, height and weight. Among 21 TWs with signs of kidney damage, there were four individuals who received potentially nephrotoxic chemotherapeutic agents. In the other four TWs who received potentially nephrotoxic chemotherapeutic agents, signs of kidney damage on sonographic examination were not observed.

Radiation therapy was performed during treatment of 22 TWs (41, 5%). In four cases, the solitary kidney was in the field of irradiation. The dose of irradiation did not exceed 20 Gy. Two of these four individuals also received potentially nephrotoxic chemotherapeutic agents.

Discussion

Individuals with a solitary kidney are a specific group of patients. In recent years, there has been an ongoing discussion about kidney damage in patients with SFK [23, 24, 25, 26]. According to Schreuder's study, being born with or having an acquiring SFK in childhood results in ongoing glomerular hyperfiltration and in renal injury with hypertension and albuminuria before adulthood in over 50% of those affected [23]. On the other hand, P. Marzuillo and C. Polito evaluated a cohort of 306 congenital SFK patients with prenatal diagnosis and enrollment within the first 3 months of life, and showed that the prevalence of renal damage was 3, 9%, with a cumulative proportion of 93, 7% free from renal injury at 17 years of age [24]. But, as Schreuder emphasized, both cohorts were different – in the Marzuillo and Polito's study all children were diagnosed antenatally or shortly after birth,

whereas in Schreuder's study the congenital SFK was diagnosed later in life. Both groups differed in prevalence of high blood pressure, which was present in 0, 6% of the Marzuillo's cohort and in 18, 1% in Schreuder's study [26].

Most of the patients who have been cured from TW have one kidney and they seem to be particularly at risk of kidney damage because of their exposition to additional risk factors, such as anticancer treatment. However, the typical chemo- and radiotherapy used in TW treatment does not generally cause severe renal injury [8, 27]. According to SIOP rules, only high-risk patients or in stage IV are treated with nephrotoxic cytostatics, such as carboplatin and cyclophosphamide [3]. Bilateral TWs are also at higher risk of CKD [8].

Then the assessment of SFK in TWs is very important. The follow-up of TWs includes physical examination with measurement of BP, abdomen ultrasound, and a serum creatinine and urine test [3].

Hyperechoic rings around renal pyramids on sonographic examination, observed in 41, 5% of TWs, may indicate impairment of renal tubules. Hyperechoic rings around renal pyramids might be the outcome of one of the following: primary hypercalciuria, hypercalcemia with hypercalciuria, hyperparathyroidism, or tubular acidosis [28, 29, 30]. Hyperechoic rings around renal pyramids are the outcome of the accumulation of calcium deposit in the distal and collecting tubules [31]. According to the theory of Anderson-Carr, hyperechoic rings around renal pyramids appear initially before formation of renal calculi [32]. Hyperechoic rings may be an ultrasound sign of early nephrocalcinosis [33, 34]. In all TWs with hyperechoic rings around renal pyramids, further diagnosis focusing on tubular impairment is necessary. The mean values of RI in TWs didn't exceed normal values. Hyperechoic rings around renal pyramids might even precede modification in the parenchymal microvasculature due to normal values of RI.

In our sample increased cortex echogenicity was observed in six TWs (11, 3%). This is a nonspecific sonographic marker of acute and chronic changes in glomeruli or renal parenchyma [35, 36]. Cortex echogenicity correlated with histological changes in renal parenchyma and with tubular atrophy [37, 38].

Renal scars were more common in TWs (4 - 7, 5%). There were no scars observed in the control group (no statistical significance). The presence of these signs may be an outcome of urinary tract infection during immunosuppression. Renal scars appear directly over calyces and are associated with parenchymal thickening [39].

Renal calculi were detected in 3 TWs (5, 6%). None of the individuals in the control group had renal calculi diagnosed. In two cases, time from the end of treatment was relatively short - four and ten months. Renal calculi might be a consequence of chemotherapy. According to Palmer et al., the sensitivity of ultrasound examination for detection of renal calculi was 89% in comparison to that for computed tomography, which was 100% [40]. Thus, the true prevalence of nephrolithiasis might be more frequent than that presented in this study.

In the present study, hypertrophy of the solitary kidney was observed in thirty-eight (71, 7%) TWs. In an English study, Bailey reported compensatory renal hypertrophy in 38/40 patients [41]. Neu et al. detected compensatory contralateral renal hypertrophy in 88, 3% of TWs [42]. The mean percent of expected renal length in the TWs group was 118%, while in the control group, the value of expected renal length was nearly 100%. In a study by Di Tullio et al., the mean length of the solitary kidney was 128% of the reference value [9]. The study was repeated after six years, and there were no significant differences in length and volume of the kidney [10]. Similar values were observed by Krawczuk-Rybak et al. [12]. In a study by Levitt et al., hypertrophy of the solitary kidney was observed in 55% of individuals [11]. Zerlin et al. observed hypertrophy of the solitary kidney in 50% of TWs [13]. Kishore reported compensatory hypertrophy in 8/29 TWs and subnormal renal size in one TWs [43].

In TWs, mean eGFR was significantly lower than that of the control group. Six TWs (11, 3%) had eGFR below 90 ml/min/1,73 m². Di Tullio et al. and Indolfi et al. did not observe decreased eGFR, as assessed with the Schwartz formula [9, 10]. These results are similar to findings of Srinivas et al. and Chevallier et al., who did not observe decreased eGFR, measured

with inulin clearance [14, 44]. In study by Levitt et al., GFR below 80 ml/min/1.73 m², measured as 51 Cr EDTA clearance, was detected in 19% of cases [11]. Decreased GFR below 80 ml/min/1.73 m² was also observed in 43% individuals, according to Krawczuk-Rybak et al. [12]. By contrast, increased GFR was reported by Stronska et al. and Donckerwolck et al. [45, 46]. Cozzi reported that TWs aged 33 to 51 years showed significantly progressive decrease in eGFR (mean ± SD 88, 1±22, 6 during the third decade after surgery vs. 66, 6±15, 6 ml/min/1.73 m² during the fifth decade after surgery, p=0.02) [47]. According to Kern, longer follow-up may reveal clinically significant declines in renal function occurring years following nephrectomy [48].

In the present study, increased albumin excretion, measured as ACR over 30 mg/g, was observed in 13, 2% of TWs. Prevalence of albuminuria in the published literature ranges from 9% (Levitt et al.) to 84% (Srinivas et al.) [9, 10, 11, 14, 44].

In the present study, there was no correlation between the percent of expected renal length and sonographic and laboratory parameters. In a study by Di Tullio, the length of the solitary kidney inversely correlated with age at time of diagnosis, and kidney volume directly correlated with microalbuminuria [9]. Levitt did not observe a correlation of renal length with eGFR, microalbuminuria, SBP or treatment of TW [11]. There were no correlations between sonographic findings and laboratory tests in a study by Krawczuk-Rybak et al. [12]. Zerlin did not observe a correlation between the prevalence of renal hypertrophy and age at time of nephrectomy, stage of tumour or treatment of TW [13].

This study analysed the risk of CKD in TWs. Nephrectomy was one of the risk factors for CKD in TWs. Six TWs might be classified as stage II of CKD. According to Stefanowicz et al., 56, 25% and 43, 75% of TWs were diagnosed as stage I and II of CKD, respectively [16]. However, according to Interiano et al., the current guidelines do not recognize solitary kidney as a structural abnormality [49]. However, further studies are needed to determine whether the absence of one kidney is a marker for CKD development [49]. In the Neu TWs study, 21/34 (62%) TWs (mean age 28.7 years, mean follow-up 24.8 years) had CKD stages I-III, based on cystatin-related eGFR [42]. The reason for those differences was the method of GFR estimation. In the present study, classification was based on estimated GFR, while in the study by Stefanowicz et al., GFR was assessed as clearance of 99 Tc-DTPA [16]. Classification of CKD underlines the risk of deterioration of renal function. The end stage of renal disease twenty years after the treatment for Wilms tumour is rather low: 0, 6%, according to Breslow et al. [50].

There were differences in the sonographic and laboratory parameters between TWs who received and did not receive potentially nephrotoxic chemotherapeutic agents (carboplatin, cisplatin, ifosfamide, or cyclophosphamide). Potentially nephrotoxic chemotherapeutic agents were administered for high risk histology and stages III and IV of TW. There were no differences in the distribution of stage of TW between individuals with and without sonographic signs of kidney damage. These findings can be explained by the fact that according to SIOP guidelines, cisplatin was exchanged for the potentially less nephrotoxic carboplatin, and ifosfamide was exchanged for the less nephrotoxic cyclophosphamide. Additionally, according to SIOP 2001, carboplatin is administered in six cycles. Each cycle lasts for three days with a daily dose of 200 mg/m² [3]. Previously, carboplatin was administered one day with a dose of 600 mg/m².

Radiation therapy in the field of the solitary kidney was performed in four TWs (7, 5%) enrolled in our study. Two of these TWs additionally received potentially nephrotoxic chemotherapy. Those individuals were treated according to the SIOP 93-01 and SIOP 9 protocols. In the present study, sonographic and laboratory parameters were not compared among groups who received and did not receive irradiation to the field of the solitary kidney because of disproportion in groups - 4 vs 49. De Graff et al. observed lower values of GFR and renal plasma flow (RPF) in TWs who underwent irradiation in comparison to those who did not undergo irradiation of the solitary kidney [51].

Hypertension may be an early indicator of renal dysfunction in TWs. The prevalence of arterial hypertension was diagnosed in six TWs (11, 3%). None of the individuals in the control group had arterial hypertension diagnosed. None of the individuals enrolled in the study had antihypertensive drugs administered. According to other authors, the prevalence of hypertension in TWs was 11-29% [11, 52]. In the Neu study, 40% of TWs had arterial hypertension [42]. Arterial hypertension is not a diagnostic criterion of CKD, but it can increase the risk of deterioration of eGFR and cardiovascular complications [6]. Lubrano et al. showed that patients with acquired SFK due to previous monolateral total nephrectomy due to trauma over a 14-year follow-up had significant increases in hypertension (12% vs 52, 9%) [53]. In view of this fact, it is necessary to monitor BP every six months. Some authors recommended BP monitoring at least every five years [54], but in our opinion, this is too infrequent.

Is solitary kidney a risk factor for renal injury or chronic kidney disease? We believe this is an open question. Although current NKF guidelines do not recognize SFK as a structural abnormality [6], several studies suggest that SFK is a risk factor for the progression of CKD [44, 55, 56]. Kolvek et al. demonstrated that a substantial proportion of children with SFK developed renal injury defined as hypertension, severely increased albuminuria and a significantly impaired eGFR and/or use of antihypertensive or antiproteinuric medications during childhood (median age 11,0 years). This was especially true for those with CAKUT (congenital anomalies of the kidney and the urinary tract) in the SFK [57]. Mavinkurve-Groothuis et al. showed that during follow-up, mean eGFR and BP z-scores remained stable at an acceptable level, but in the group of 31 TWs with follow-up of 15 years, only 23% showed signs of renal injury (defined as eGFR < 60 ml/min/1,73 m², proteinuria and/or high BP, and/or drug use to treat either proteinuria and/or high BP) vs 54% in a group of SFK patients based on non-oncological causes (p=0,0004) [58]. According to KDIGO recommendations, CKD is defined as abnormalities of kidney structure or function, present for > 3 months with implications for health. CKD is classified based on cause, GFR category (G1-G5), and albuminuria category (A1-A3), abbreviated CGA [6]. In our group of TWs, six (11, 3%) had values of eGFR below 90 ml/min/1,73 m² – G2 category. Increased albumin urine excretion (ACR > 30 mg/g) was observed in 7 TWs (13, 2%), 6 in the A2 category and 1 in the A3 category, risk category: G1A2 (moderately increased risk) – 6, G2A2 (high risk) – 1. Schiavetti et al. examined 35 TWs and diagnosed CKD in 3 TWs, of G2A2 category (1) and G1A2 category (2), and detected signs of kidney damage on USG in 1 TWs [59].

The limitations of this study are as follows: 1. Colorimetric-modified Jaffe method of creatinine serum concentration measurement: this factor influenced the choice of formulas to calculate eGFR, according to KDOQI guidelines. 2. Heterogeneity of the TWs group: children with differences in stages and histology. These conditions have an influence on the type of treatment (chemo- and/or no radiotherapy) that might be an additional factor for kidney damage. 3. Controls were patients with both kidneys.

Conclusion

Ultrasonographic abnormalities in solitary kidneys of TWs are frequent. The most frequently detected anomalies in SFK in TWs are hyperechoic rings around renal pyramids. In TWs sonographic examination is ought to be performed, not only to diagnose tumour recurrence and to assess hypertrophy, but also to assess the signs of kidney damage and their progression.

Disclosure Statement

No conflicts of interest, financial or otherwise are declared by the authors.

References

- 1 Kaste SC, Dome JS, Babyn PS, Graf NM, Grundy P, Godzinski J, Levitt GA, Jenkinson H: Wilms tumour: prognostic factors, staging, therapy and late effects. *Pediatr Radiol* 2008;38:2-17.
- 2 Fernandez CV, Geller JI, Ehrilch PF, Hill DA, Kalapurakal JA, Dome JS: Renal tumors; in Pizzo PA, Poplack DG (eds): *Principles and Practice of Pediatric Oncology*. Philadelphia, Baltimore, New York, London, Buenos Aires, Hong Kong, Sydney, Tokyo, Wolters Kluwer, 2016, pp 753-771.
- 3 SIOP: Recommendations for longterm follow-up of children with renal neoplasms. *Nephroblastoma Clinical Trial and Study Protocol*, 2001;Appendix 7:161-162. URL: <https://www.skion.nl/workspace/uploads/Protocol-SIOP-2001.pdf>.
- 4 Brisse HJ, Smets AM, Kaste SC, Owens CM: Imaging in unilateral Wilms tumour. *Pediatr Radiol* 2008;38:18-29.
- 5 National Kidney Foundation K/DOQI: URL: https://www.kidney.org/sites/default/files/docs/ckd_evaluation_classification_stratification.pdf
- 6 KDIGO: 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. URL: http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.
- 7 Bardi E, Olah AV, Bartyik K, Endreffy E, Jenei C, Kappelmayer J, Kiss C: Late effects on renal glomerular and tubular function in childhood cancer survivors. *Pediatr Blood Cancer* 2004;43:668-673.
- 8 Stefanowicz J, Kosiak M, Kosiak W, Lipska-Ziękiewicz B: Chronic kidney disease in Wilms tumour survivors – what do we know today?; in Van del Heuvel-Eibrink MM (ed): *Wilms tumor Australia*, Codon Publications, 2016, pp 131-145.
- 9 Di Tullio MT, Casale F, Indolfi P, Polito C, Giuliano M, Martini A, Cimmaruta E, Morgera C, Cioce F, Greco N: Compensatory hypertrophy and progressive renal damage in children nephrectomized for Wilms tumor. *Med Pediatr Oncol* 1996;26:325-328.
- 10 Indolfi P, Di Tullio MT, Casale F, De Rosa E, Polito C, Cioce F: Letter to the Editor: Kidney Size and Function After Unilateral Nephrectomy for Wilms Tumor: A Longitudinal Study. *Med Pediatr Oncol* 2001;37:485-486.
- 11 Levitt GA, Yeomans E, Dicks Mircaux C, Breatnach F, Kingston J, Pritchard J: Renal size and function after cure of Wilms tumor. *Br J Cancer* 1992;66:877-882.
- 12 Krawczuk-Rybak M, Kuźmich M, Kitszel A, Wysocka J, Zalewska B, Olszewska M: Renal function and size after complex treatment of Wilms' tumour. *Med Wieku Rozwoj*. 2003;7:359-367.
- 13 Zerlin JM, Haliloglu M, Cohen MD: Growth of the solitary kidney after nephrectomy in children with unilateral Wilms tumor. *Pediatr Radiol* 1996;26:547-552.
- 14 Srinivas M, Agarwala S, Padhy AK, Gupta AK, Bajpai M, Bhatnagar V, Gupta DK, Mitra DK: Somatic growth and renal function after unilateral nephrectomy for Wilms' tumor. *Pediatr Surg Int* 1998;14:185-188.
- 15 Stefanowicz J, Kosiak M, Kosiak W, Korbus-Kosiak A, Sierota D, Owczuk R: Cystatin C and parenchymal thickness/kidney length ratio in Wilms tumor survivors. *Pediatr Blood Cancer* 2010;54:41-46.
- 16 Stefanowicz J, Kosiak M, Romanowicz G, Owczuk R, Adamkiewicz-Drożyńska E, Balcerska A: Glomerular filtration rate and prevalence of chronic kidney disease in Wilms' tumour survivors. *Pediatr Nephrol* 2011;26:759-766.
- 17 Chen JJ, Pugach J, Patel M, Luisiri A, Steinhardt GF: The renal length nomogram: a multivariable approach. *J Urol* 2002;168:2149-2152.
- 18 MrNomogram: Multivariable Pediatric Renal Nomogram. URL: <https://www.prevmed.sunysb.edu/jjc/MrNomogram/Default.aspx>.
- 19 Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;58:259-263.
- 20 Walser M: Assessing renal function from creatinine measurements in adults with chronic renal failure. *Am J Kidney Dis* 1998;32:23-31.

- 21 Keane WF, Eknoyan G: Proteinuria, albuminuria, risk assessment, detection, elimination (PARADE): a position paper of the National Foundation. *Am J Kidney Dis* 1999;33:1004-1010.
- 22 National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114:555-576.
- 23 Schreuder MF: Life with one kidney. *Pediatr Nephrol* 2018;33:595-604.
- 24 Marzuillo P, Guarino S, Grandone A, Di Somma A, Della Vecchia N, Esposito T, Macchini G, Marotta R, Apicella A, Diplomato M, Rambaldi PF, Perrone R, Miraglia del Giudice E, La Manna A, Polito C: Outcomes of a cohort of prenatally diagnosed and early enrolled patients with congenital solitary functioning kidney. *J Urol* 2017;198:1153-1158.
- 25 Marzuillo P, Polito C: Congenital solitary kidney in childhood: not so bad. *Pediatr Nephrol* 2018;33:723-724.
- 26 Schreuder MF: Life with one kidney: response to comments by Marzuillo and Polito. *Pediatr Nephrol* 2018;33:725-726.
- 27 Skinner R: Late renal toxicity of treatment for childhood malignancy: risk factors, long-term outcomes, and surveillance. *Pediatr Nephrol* 2018;33:215-225.
- 28 Hernanz-Schulman M: Hyperechoic renal medullary pyramids in infants and children. *Radiology* 1991;181:9-11.
- 29 Jequier S, Kaplan BS: Echogenic renal pyramids in children. *J Clin Ultrasound* 1991;19:85-92.
- 30 Shultz PK, Strife JL, Strife CF, McDaniel JD: Hyperechoic renal medullary pyramids in infants and children. *Radiology* 1991;181:163-167.
- 31 Saarela T, Lanning P, Koivisto M: Prematurity-associated nephrocalcinosis and kidney function in early childhood. *Pediatr Nephrol* 1999;13:886-890.
- 32 Paivansalo MJ, Kallioinen MJ, Merikanto JS, Jalovaara PK: Hyperechogenic „rings” in the periphery of renal medullary pyramids as a sign of renal disease. *J Clin Ultrasound* 1991;19:283-287.
- 33 Al-Murrani B, Cosgrove DO, Svensson WE, Blaszczyk M: Echogenic rings - an ultrasound sign of early nephrocalcinosis. *Clin Radiol*. 1991;44:49-51.
- 34 Shavit L, Jaeger P, Unwin RJ: What is nephrocalcinosis? *Kidney Int* 2015;88:35-43.
- 35 Huntington DK, Hill SC, Hill MC: Sonographic manifestation of medical renal disease. *Semin Ultrasound CT MR*. 1991;12:290-307.
- 36 Hricack H, Cruz C, Romanski R, Uniewski MH, Levin NW, Madrazo BL, Sandler MA, Eyler WR: Renal parenchymal disease: sonographic-histologic correlation. *Radiology* 1982;144:141-147.
- 37 Rosenfield AT, Siegel NJ: Renal parenchymal disease: histopathologic-sonographic correlation. *AJR Am J Roentgenol* 1981;137:793-798.
- 38 Quaia E, Bertolotto M: Renal parenchymal disease: is characterization feasible with ultrasound? *Eur Radiol* 2002;12:2006-2020.
- 39 Chu WCW: Renal Junction Line; in Ahuja AT (ed): *Diagnostic Imaging: Ultrasound*. Salt Lake City, Utah, Amirsys, 2007, chapter 5, pp 9.
- 40 Palmer JS, Donaher ER, O’Riordan MA, Dell KM: Diagnosis of pediatric urolithiasis: role of ultrasound and computerized tomography. *J Urol* 2005;174:1413-1416.
- 41 Bailey S, Roberts A, Brock C, Price L, Craft AW, Kilkarni R, Lee RE, Skillen AW, Skinner R: Nephrotoxicity in survivors of Wilms’ tumours in the North of England. *Br J Cancer* 2002;87:1092-1098.
- 42 Neu MA, Russo A, Wingerter A, Alt F, Theruvath J, El Malki K, Kron B, Dittrich M, Lotz J, Stein R, Beetz R, Faber J: Prospective analysis of long-term renal function in survivors of childhood Wilms tumor. *Pediatr Nephrol*. 2017;32:1915-1925.
- 43 Kishore SS, Oberoi S, Bhattacharya A, Prasad R, Trehan A, Bansal D, Marwaha RK: Function and size of the residual kidney after treatment of Wilms tumor. *Pediatr Hematol Oncol* 2015;32:11-17.
- 44 Chevallier C, Hadj-Aissa A, Brunat-Mentigny M, Faraj G, Schell M, Cochat P: Renal function after nephrectomy for Wilms’ tumor. *Arch Pediatr* 1997;7:639-644.
- 45 Strońska E, Zwolińska D, Sawicz-Birkowska K, Makulska I, Magier K, Czernik J: Assessment of function of the only kidney in children after nephrectomy due to Wilms’ tumour. *Pol Merkur Lekarski* 2003;14:311-314.

- 46 Donckerwolcke RM, Coppes MJ: Adaptation of renal function after unilateral nephrectomy in children with renal tumors. *Pediatr Nephrol* 2001;16:568-574.
- 47 Cozzi DA, Ceccanti S, Cozzi F: Renal function up to the 5th decade of life after nephrectomy in childhood: a literature review. *Nephrology (Carlton)* 2018;23:397-404.
- 48 Kern AJ, Inoue B, Ko JS, Gorin MA, Allaf ME, Goldstein S, DiCarlo HN, Shah BB, Wang MH: Impact of nephrectomy on long-term renal function in non-syndromic children treated for unifocal Wilms tumor. *J Pediatr Urol* 2014;10:662-666.
- 49 Interiano RB, Delos-Santos N, Huang S, Srivastava DK, Robinson LL, Hudson MM, Green DM, Davidoff AM: Renal function in survivors of nonsyndromic Wilms tumor treated with unilateral radical nephrectomy. *Cancer* 2015;121:2449-2456.
- 50 Breslow NE, Collins AJ, Ritchey M L, Grigoriev YA, Peterson SM, Green DM: End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. *J Urol* 2005;174:1972-1975.
- 51 de Graaf SS, van Gent H, Reitsma-Bierenes WC, van Luyk WH, Dolsma WV, Postma A: Renal function after unilateral nephrectomy for Wilms tumor: the influence of radiation therapy. *Eur J Cancer* 1996;32A:465-469.
- 52 Barrera M, Roy LP, Stevens M: Long-term follow-up after unilateral nephrectomy and radiotherapy for Wilms' tumour. *Pediatr Nephrol* 1989;3:430-432.
- 53 Lubrano R, Gentile I, Falsaperla R, Vitaliti G, Marcellino A, Elli M: Evolution of blood pressure in children with congenital and acquired solitary functioning kidney. *Ital J Pediatr* 2017;43:43.
- 54 Spreafico F, Terenziani M, Testa S, Perotti D, Collini P, Piva L, Ardisino G: Long-term renal outcome in adolescent and young adult patients nephrectomized for unilateral Wilms tumor. Letter to the Editor. *Pediatr Blood Cancer* 2014;61:1136-1137.
- 55 Cozzi DA, Ceccanti S, Frediani S, Schiavetti A, Cozzi F: Chronic kidney disease in children with unilateral renal tumor. *J Urol* 2012;187:1800-1805.
- 56 Cozzi DA, Ceccanti S, Frediani S, Mele E, Cozzi F: Renal function adaption up to fifth decade after treatment of children with unilateral renal tumor: a cross sectional and longitudinal study. *Pediatr Blood Cancer* 2013;60:1534-1538.
- 57 Kolvek G, Podracka L, Rosenberger J, Stewart RE, van Dijk JP, Reijnveld SA: Solitary functioning kidney in children – a follow up study. *Kidney Blood Press Res* 2014;39:272-278.
- 58 Mavinkurve-Groothuis AM, van de Kracht F, Westland R, van Wijk JA, Loonen JJ, Screuder MF: Long-term follow-up of blood-pressure and glomerular filtration rate in patients with a solitary functioning kidney: a comparison between Wilms tumor survivors and nephrectomy for other reasons. *Pediatr Nephrol* 2016;31:435-441.
- 59 Schiavetti A, Altavista P, De Luca L, Andreoli G, Megaro G, Versacci P: Long-term renal function in unilateral non-syndromic renal tumor survivors treated according to International Society of Pediatric Oncology Protocols. *Pediatr Blood Cancer* 2015;62:1637-1644.