NEPHROLOGICAL PROBLEMS IN CHILDREN WITH TUBEROUS SCLEROSIS COMPLEX – A SINGLE-CENTER EXPERIENCE

Problemy nefrologiczne u dzieci chorujących na stwardnienie guzowate – doświadczenie jednego ośrodka

Anna Maria Wabik[1], Wiktoria Suszek[2], Agnieszka Piróg[2], Mariusz I. Furmanek[3], Piotr Skrzypczyk[1]

1. *Department of Pediatrics and Nephrology, Medical University of Warsaw, Poland*
2. *Student Scientific Group at the Department of Pediatrics and Nephrology, Medical University of Warsaw, Poland*
3. *Department of Pediatric Radiology, Medical University of Warsaw, Poland*

Anna Maria Wabik – 0009-0007-3339-8157
Wiktoria Suszek – 0009-0000-6702-6166
Agnieszka Piróg – 0009-0003-5422-8692
Mariusz I. Furmanek – 0000-0002-6713-6338
Piotr Skrzypczyk – 0000-0002-1959-8255

Abstract

Introduction and objective: Tuberous sclerosis complex is a rare genetic disorder characterized by benign tumours in multiple organs (e.g., brain, kidneys). The affected patients present with kidney tumours, including angiomyolipomas and cysts, rarely other lesions, including renal cell carcinoma. This study aimed to evaluate renal lesions, renal function, and blood pressure in children managed in our Centre between 2018 and 2023. **Materials and methods:** We looked at the presence and size of kidney lesions (ultrasonography, magnetic resonance), genetic findings, blood pressure, and biochemical parameters, including kidney function (GFR calculated from the Schwartz formula) in 55 pediatric patients (28 boys, 27 girls, 8.1 ± 4.6 years). **Results:** Angiomyolipomas were found in 40/55 (72.7%) patients, including fat-poor (atypical) angiomyolipomas in 9 (16.4%) children. The mean angiomyolipoma size was 13.1 ± 15.1 mm; large angiomyolipomas ≥30 mm were present in 5 (9.1%) children. Cysts were found in 46 (83.6%) children; the mean cyst size was 10.3 ± 12.3 mm. The largest cysts (up to 75 mm) were found in 4 children with contiguous gene syndrome (deletion involving two genes: *TSC2* and *PKD1*). Seven (12.7%) children had arterial hypertension, including 3 out of 4 children with contiguous gene syndrome. Mean GFR was 111.2 ± 17.1 mL/min/1,73 m², and GFR <90 mL/min/1,73 m² was found in 3 (5.5%) children (2 with contiguous gene syndrome). Patients with hypertension had higher triglyceride concentrations, larger kidney longitudinal dimensions, and larger cysts (22.6 ± 27.1 vs. 8.0 ± 5.3 mm). The size of angiomyolipoma correlated with age (r = 0.470, p <0.001) and urinary albumin-creatinine ratio (r = 0.444, p = 0.001). **Conclusions:** 1. Large renal lesions are common already in children with tuberous sclerosis complex, with the most severe renal manifestations found in patients with contiguous gene syndrome. 2. The size of angiomyolipoma increases with age in children with tuberous sclerosis complex. 3. Large angiomyolipomas are risk factors for elevated urinary albumin excretion. 4. In paediatric patients with tuberous sclerosis complex, large cysts are risk factors for arterial hypertension. 5. Paediatric nephrologists should follow up all pediatric patients with tuberous sclerosis complex.

Streszczenie

Wprowadzenie i cel: Stwardnienie guzowate jest rzadką chorobą genetyczną, charakteryzującą się występowaniem zmian guzowatych w wielu narządach (np. w mózgu, nerkach). U pacjentów występują guzy nerek zwane naczyniakomięśniakotłuszczakami oraz torbiele, rzadko inne zmiany, w tym rak nerki. Celem pracy jest ocena zmian w nerkach, funkcji nerek i ciśnienia tętniczego u dzieci będących pod opieką ośrodka w latach 2018–2023. **Materiał i metody:** W grupie 55 dzieci (28 chłopców, 27 dziewczynek, 8,1 ± 4,6 lat) analizowano obecność i wielkość zmian w nerkach (w badaniu ultrasonograficznym i rezonansie magnetycznym), wynik badania genetycznego, ciśnienie tętnicze oraz parametry biochemiczne, w tym funkcję nerek (GFR według wzoru Schwartza). **Wyniki:** Naczyniakomięśniakotłuszczaki stwierdzono w nerkach u 40 (72,7%) pacjentów, w tym atypowe (ubogotłuszczowe) – u 9 (16,4%). Średnia wielkość guza wynosiła 13,1 ± 15,1 mm; guzy ≥30 mm wykryto u 5 (9,1%) dzieci. Torbiele nerek rozpoznano u 46 (83,6%) dzieci. Średnia wielkość torbieli wynosiła 10,3 ± 12,3 mm. Największe (do 75 mm) wykryto u 4 dzieci z zespołem genów sąsiadujących (delecja obejmująca geny TSC2 i PKD1). Nadciśnienie tętnicze stwierdzono u 7 (12,7%) dzieci, w tym u 3 z 4 dzieci z zespołem genów sąsiadujących. Średni GFR wynosił 111,2 ± 17,1 ml/min/1,73 m², a GFR <90 ml/min/1,73 m² stwierdzono u 3 (5,5%) dzieci (2 z zespołem genów sąsiadujących). Pacjenci z nadciśnieniem tętniczym mieli wyższe stężenie trójglicerydów, większy wymiar podłużny nerek i większe torbiele (22,6 ± 27,1 vs. 8,0 ± 5,3 mm). Rozmiar naczyniakomięśniakotłuszczaka korelował dodatnio z wiekiem (r = 0,470, p <0,001) oraz wskaźnikiem albuminowo-kreatyninowym w moczu (r = 0,444, p = 0,001). **Wnioski:** 1. Zmiany w nerkach są powszechne u dzieci ze stwardnieniem guzowatym, a najbardziej nasilone objawy nerkowe występują u pacjentów z zespołem genów sąsiadujących. 2. U dzieci ze stwardnieniem guzowatym wymiar naczyniakomięśniakotłuszczaków

rośnie z wiekiem. 3. Naczyniakomięśniakotłuszczaki o dużym wymiarze są czynnikiem ryzyka zwiększonego wydalania albumin z moczem u tych chorych. 4. U dzieci ze stwardnieniem guzowatym duży wymiar torbieli stanowi czynnik ryzyka nadciśnienia tętniczego. 5. Wszyscy pacjenci pediatryczni ze stwardnieniem guzowatym powinni być objęci opieką nefrologa dziecięcego.

Keywords: children; blood pressure; tuberous sclerosis complex; angiomyolipoma; renal cyst

Słowa kluczowe: dzieci; ciśnienie tętnicze; stwardnienie guzowate; naczyniakomięśniakotłuszczak; torbiel nerki

DOI 10.53301/lw/204280

Received: 03.01.2025

Accepted: 23.04.2025

Corresponding author:
Piotr Skrzypczyk
Department of Paediatrics and Nephrology,
Medical University of Warsaw,
63a Żwirki i Wigury Str., 02-091 Warsaw
e-mail: pskrzypczyk@wum.edu.pl

Introduction

Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder with a prevalence of approximately 1:5800 live births [1]. It is caused by pathogenic *TSC1* (9q34) or *TSC2* variants. The protein products of the *TSC1* (hamartin) and *TSC2* (tuberin) genes form a complex that physiologically inhibits the mTOR (mammalian target of rapamycin) protein kinase, whose proper function is to regulate cell division, differentiation, and migration. Inactivation of the *TSC1* or *TSC2* gene leads to over-activation of the mTOR pathway, which manifests as nodular lesions across virtually all organs. The pathogenic variant is detected *de novo* in 70–80% of patients; in the remaining cases, the disease is inherited in an autosomal dominant manner [2]. The International Tuberous Sclerosis Complex Consensus Group diagnostic criteria for TSC, updated in 2021, are presented in Table 1 [1].

Renal manifestations occur in approximately 80% of individuals with TSC. They are the second most common cause of morbidity and mortality across all age groups and the leading cause of death in patients >30 years of age [3]. Angiomyolipoma (AML) is the most frequent renal complication of TSC. The detection rate of AML increases with age, ranging from 8.8% in children under 2 years to 78.9% in adults over 40 years [4]. AMLs belong to a group of benign tumours derived from perivascular epithelioid tissue (PEComa, PEC tumours) [5]. They are composed of aneurysmal vessels, smooth muscle fibres, and mature adipose tissue. A fat-poor AML is a variant that is difficult to differentiate from renal cancer [6]. Renal cysts are found in 10–20% of children and 14–45% of adults and are usually asymptomatic. Renal cancer may occur in 6% of patients with TSC, including children. It is characterized by slow growth and very rare distant metastasis [7].

Our Centre has been treating nephrological manifestations in TSC children across Poland since 2018. The aim of this study was to assess changes in renal size and function, as well as blood pressure in a group of children managed in our institution between 2018 and 2023.

Materials and methods

This retrospective study included 55 children (28 boys and 27 girls) with a confirmed diagnosis of TSC based on the current 2021 Criteria, who received renal treatment between 2018 and 2023 [1].

Before initiating the study, approval was obtained from the local ethics committee (approval no. KB/145/2017, July 4, 2017). All procedures were performed in accordance with the ethical standards of the local ethics committee and the Declaration of Helsinki. Informed consent to participate in the study was obtained from the legal

Table 1. The International TSC Diagnostic Criteria [1] in our own modification. A definite clinical diagnosis of TSC can be established in a proband with two major features or one major feature with two or more minor features, or a pathogenic TSC1 or TSC2 variant must be detected in unaffected tissue (or blood).

Major features	Minor features
• Hypomelanotic macules (≥3; at least 5mm diameter) • Angiofibroma (≥3) or fibrous cephalic plaque • Ungual fibromas (≥2) • Shagreen patch • Multiple retinal hamartomas • Multiple cortical tubers and/or radial migration lines • Subependymal nodule (≥2) • Subependymal giant cell astrocytoma • Cardiac rhabdomyoma • Lymphangioleiomyomatosis (LAM) • Angiomyolipomas (>2) (LAM and AML is considered a single criterion)	• "Confetti" skin lesions • Dental enamel pits (>3) • Intraoral fibromas (≥2) • Retinal achromatic patch • Multiple renal cysts • Nonrenal hamartomas • Sclerotic bone lesions

guardians of all patients, as well as from the participants themselves (≥16 years of age) prior to enrolment.

The following clinical data were analysed: age (years), gender, height (cm), body weight (kg), body mass index (BMI) (kg/m²), hypertension (HT), and genetic findings (pathogenic variants in the *TSC1*, *TSC2*, and *TSC2/PKD1* genes). Anthropometric parameters were assessed using WHO [8] growth charts for the youngest children, OLA [9] charts for preschool children, and OLAF charts for school-aged children [10].

Renal imaging included ultrasound (US) in all children and magnetic resonance imaging (MRI) in 41 patients. Ultrasound (US) B-mode scans were taken using a Philips Epiq 5G system (Royal Philips, Amsterdam, The Netherlands), while T2, T1, and DWI-weighted MRI images were taken using the MAGNETOM Skyra 3T system (Siemens AG, Berlin, Germany), with and without intravenous Gadovist (gadobutrol) (Bayer AG, Leverkusen, Germany). The kidney size (calculated as the mean length of the right and left kidneys) and the presence and characteristics of renal lesions (angiomyolipomas, cysts, and other abnormalities) were evaluated. For angiomyolipomas and cysts, the largest diameter of the largest lesion (mm) was recorded.

Biochemical parameters were analysed: serum creatinine (mg/dL), cystatin C (mg/L), uric acid (mg/dL), total cholesterol (mg/dL), cholesterol fractions (mg/dL), and triglycerides (mg/dL). Glomerular filtration rate (GFR) was calculated using the creatinine and creatinine-cystatin Schwartz formula (mL/min/1.73 m²) [11]. Elevated uric acid levels were defined as ≥5.5 mg/dL according to Feig [12]. Total cholesterol was considered elevated at ≥200 mg/dL, and triglycerides at ≥100 mg/dL in children aged 0–9 years and ≥130 mg/dL in children aged 10–18 years [13]. Increased (abnormal) albuminuria was defined as an albumin-creatinine ratio (ACR) ≥30 mg/g [14].

Statistical analysis of the obtained results was performed using TIBCO Statistica 13.3 (TIBCO Software Inc., Palo Alto, CA, USA). The results were presented as mean values, standard deviation, and range. The normality of the distribution was assessed using the Shapiro–Wilk test. Comparisons between groups with a normal distribution were performed using the Student's *t*-test, while data with a non-normal distribution were compared using the Mann–Whitney *U* test. The strength of the relationship between two data sets was assessed using Pearson's linear correlation or Spearman's rank correlation, depending on the distribution. A p value <0.05 was considered statistically significant.

Results

Clinical data for TSC patients under the care of the Clinic are presented in Table 2. The study group included comparable numbers of boys and girls, with a mean age of approximately 8 years. Genetic testing was performed in more than 80% of patients. The most frequently detected pathogenic variant was located in *TSC2*, and less commonly in *TSC1*. Four patients (7.3%) had a deletion involving the *TSC2* and *PKD1* genes (a cluster of adjacent genes). Five patients (9.1%) had negative genetic tests. Ten patients (18.2%) were overweight, and none were obese.

Biochemical findings for the study group are presented in Table 3.

The mean GFR calculated using the creatinine-based formula was approximately 138 mL/min/1.73 m², with values <90 mL/min/1.73 m² observed in two children (3.6%). The creatinine-cystatin C Schwartz formula yielded a mean GFR of approximately 111 mL/min/1.73 m², with values <90 mL/min/1.73 m² identified in three children (5.5%). Uric acid levels were elevated in five patients (9.1%), total cholesterol in seven patients (12.7%), and triglycerides in ten patients (18.2%). Elevated albuminuria was detected in eleven patients (20.0%). The assessment of renal lesions in patients with TSC is presented in Table 4.

Angiomyolipomas were identified in approximately three-quarters of patients, including fat-poor lesions in nine children (16.4%). The mean AML diameter was approximately 13.1 mm, with lesions measuring ≥30 mm observed in five children (9.1%). Cysts were present in more than 80% of the patients, with an average size of approximately 10 mm. The largest cysts (up to 75 mm) were found in four children with contiguous gene syndrome

Table 2. Clinical data of patients with TSC

Number of patients (*n*)	55
Boys/girls (*n*/*n*) (%/%)	28/27 (50.9/49.1%)
Age (years)	8.1 ± 4.6 (1.6–17.8)
Genetic screening (*n*) (%) **Mutation in *TSC1* (*n*) (%)** **Mutation in *TSC2* (*n*) (%)** **Mutation in TSC2/*PKD1* (*n*) (%)** **No mutation**	45 (81.8%) 12 (21.8%) 24 (43.6%) 4 (7.3%) 5 (9.1%)
Height (cm) **Height Z-score**	131.2 ± 25.5 (81–190) 0.00 ± 1.00 (-1.96–2.30)
Body weight (kg) **Body weight Z-score**	33.1 ± 17.0 (10–76) 0.00 ± 1.00 (-1.36–2.53)
BMI (kg/m²) **BMI Z-score**	17.8 ± 3.1 (13.5–29.3) 0.83 ± 0.17 (0.58–1.47)

n – number of patients; TSC – tuberous sclerosis complex; PKD – polycystic kidney disease; BMI – body mass index

Table 3. Biochemical findings in TSC children

Parameter	Value
Creatinine (mg/dL)	0.42 ± 0.14 (0.19–0.80)
Schwartz GFR (creatinine) (ml/min/1.73 m²)	138.4 ± 31.3 (83.6–230.4)
Schwartz GFR (creatinine and cystatin C) (mL/min/1.73 m²)	111.2 ± 16.9 (72.0–156.8)
Uric acid (mg/dL)	4.1 ± 1.0 (2.4–7.6)
Total cholesterol (mg/dL)	164.7 ± 34.1 (83–294)
LDL cholesterol (mg/dL)	90.6 ± 28.5 (25.8–173.2)
HDL cholesterol (mg/dL)	57,0 ± 17,2 (10–104)
Triglycerides (mg/dL)	81.7 ± 38.0 (35–237)
ACR (mg/g)	23.12 ± 34.9 (2.7–225.7)
GFR – glomerular filtration rate; LDL – low-density lipoprotein; HDL – high-density lipoprotein; ACR – albumin/creatinine ratio	

Table 4. Renal lesions in TSC children

Parameter	Value
Number of patients (*n*)	55
Kidney size (mm)	95.2 ± 17.3 (62–155)
AMLs (n/n) (%)	40/55 (72.7%)
Fat-poor AMLs (n/n) (%)	9/55 (16.4%)
AML size (mm)	13.1 ± 14.8 (1–71)
AML ≥30 mm (n/n) (%)	5/55 (9.1%)
Renal cysts	46/55 (83.6%)
Cyst size (mm)	10.3 ± 12.3 (2 – 75)
n – number of patients; AML - angiomyolipoma	

(CGS). Figures 1 and 2 present examples of renal AMLs in children with TSC.

HT was diagnosed in seven patients (12.7%) with TSC. A comparison between normotensive and hypertensive patients is shown in Table 5. Hypertensive children exhibited higher triglycerides, larger longitudinal kidney size, and larger cysts.

A separate analysis was performed for four patients with CGS (one girl and three boys) aged 1.5 to 7.67 years, with a mean age of 4.54 ± 4.5 years (Tab. 6).

In this group, the size of the largest cyst ranged from 10 to 75 mm, with a mean of 40.3 ± 38.0 mm. GFR <90 mL/min/1.73 m² was observed in one patient (89.4 mL/min/1.73 m²). HT was found in three patients. Figure 3 presents cysts in a child with CGS.

We assessed the correlations between the severity and size of renal tumours and the remaining analysed parameters were evaluated. Positive correlations were identified only between AML size and age ($r = 0.470$, $p < 0.001$) and the ACR index ($r = 0.444$, $p = 0.001$).

Discussion

Our cross-sectional, single-centre study aimed to characterize renal manifestations in a cohort of patients with a rare, genetic disorder known as TSC. We demonstrated that TSC renal disease is common already in children, occurring in approximately 80% of patients. Cysts and AMLs are the most frequently observed abnormalities. No other renal lesions were detected in our cohort. Many patients presented with large renal lesions. Some patients exhibited HT and elevated urinary albumin excretion. Despite advanced renal involvement, the vast majority of patients had normal renal function, defined as GFR ≥90 mL/min/1.73 m².

TOSCA (Tuberous Sclerosis Registry to Increase Disease Awareness) is the largest clinical case series of TSC to date. Data from 2,093 TSC patients, including 1,324 children (63.3%), were summarized in 2017. The patients enrolled in our study at the Department of Pediatrics and Nephrology, Medical University of Warsaw constitute a group similar to the TOSCA registry in terms of gender distribution and the rates of pathogenic TSC variants (TSC2 43.6% vs. 63.3%, TSC1 21.8% vs 19.8%). The mean age of patients in the TOSCA registry was 13 years, which is higher than in our cohort [7].

In the TOSCA registry, AML lesions were present in 47.2% of patients (72.7% in our cohort), AML lesions with a diameter >3 cm were found in 41.9% (9.1% in our cohort), and renal cysts were identified in 22.8% of patients (83.6% in our cohort). In our Center, renal lesions are the main cause of admission in TSC patients, which may explain the significantly higher incidence of AMLs and cysts in the study group compared with the TOSCA registry. However, it cannot be ruled out that the higher incidence of renal lesions in our cohort resulted from the use of two imaging modalities in most patients (MRI and US), as well as a uniform, precise protocol and high-

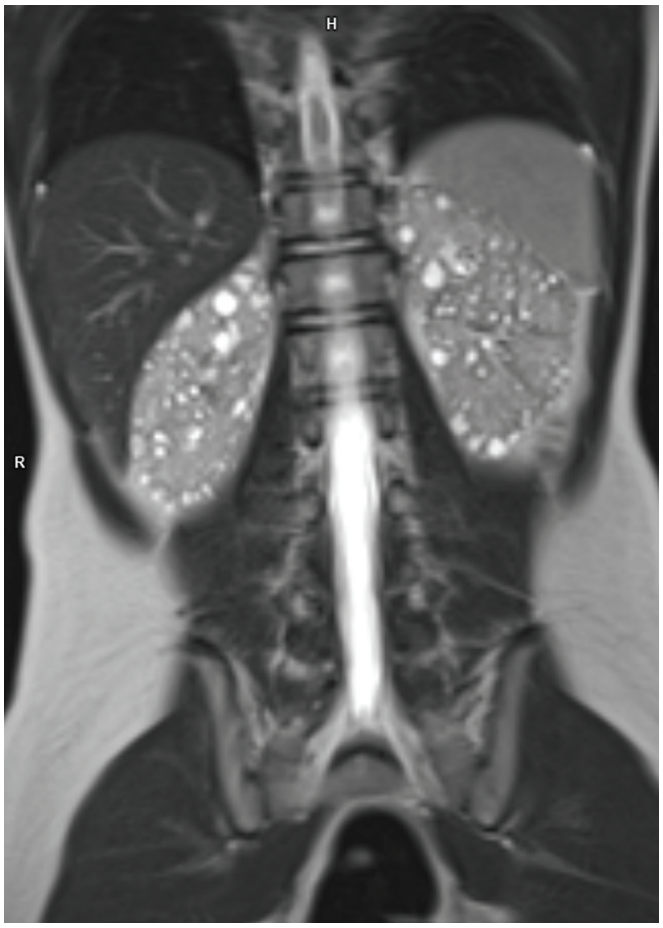

Figure 1. Small cysts in both kidneys in a child with TSC (MRI)

quality equipment (3-Tesla MRI). Similarly to the TOSCA registry, AML size correlated positively with age in our cohort [15]. AMLs, unlike CNS lesions, continue to grow throughout life in TSC patients, with a marked acceleration during adolescence. The risk of spontaneous, often massive, haemorrhage is the main risk associated with AML lesions >3 cm in diameter. Other symptoms that may result from their presence in the kidneys include pain, HT, and impaired renal function [16].

In our cohort, pathogenic *TSC2* variants predominated among genetically screened patients, which is consistent with literature reports. Defects in the *TSC2* gene are typically associated with a more severe course of the disease, particularly with more pronounced neurological symptoms [1]. The negative genetic screening in five patients (9.1%) in the study group most likely resulted from mosaicism, i.e., the presence of at least two genetic lines in a single individual: one carrying a pathogenic *TSC1* or *TSC2* variant and the other (e.g., in peripheral blood) carrying a normal variant. Mosaicism occurs in up to approximately 18% of patients with TSC [2]. In some patients, alterations in the non-coding sequences of these genes (e.g., introns) are also observed [17]. Four patients were diagnosed with *TSC2/PKD1* CGS (polycystic kidney disease with tuberous sclerosis, PKDTS), arising from the deletion of two genes (*TSC2* and *PKD1*) located in close proximity on the short arm of chromosome 16. PKDTS represents a combination of symptoms characteristic of both TSC and polycystic kidney disease (PKD). Patients with PKDTS experience rapid development of renal cysts, early renal impairment, and

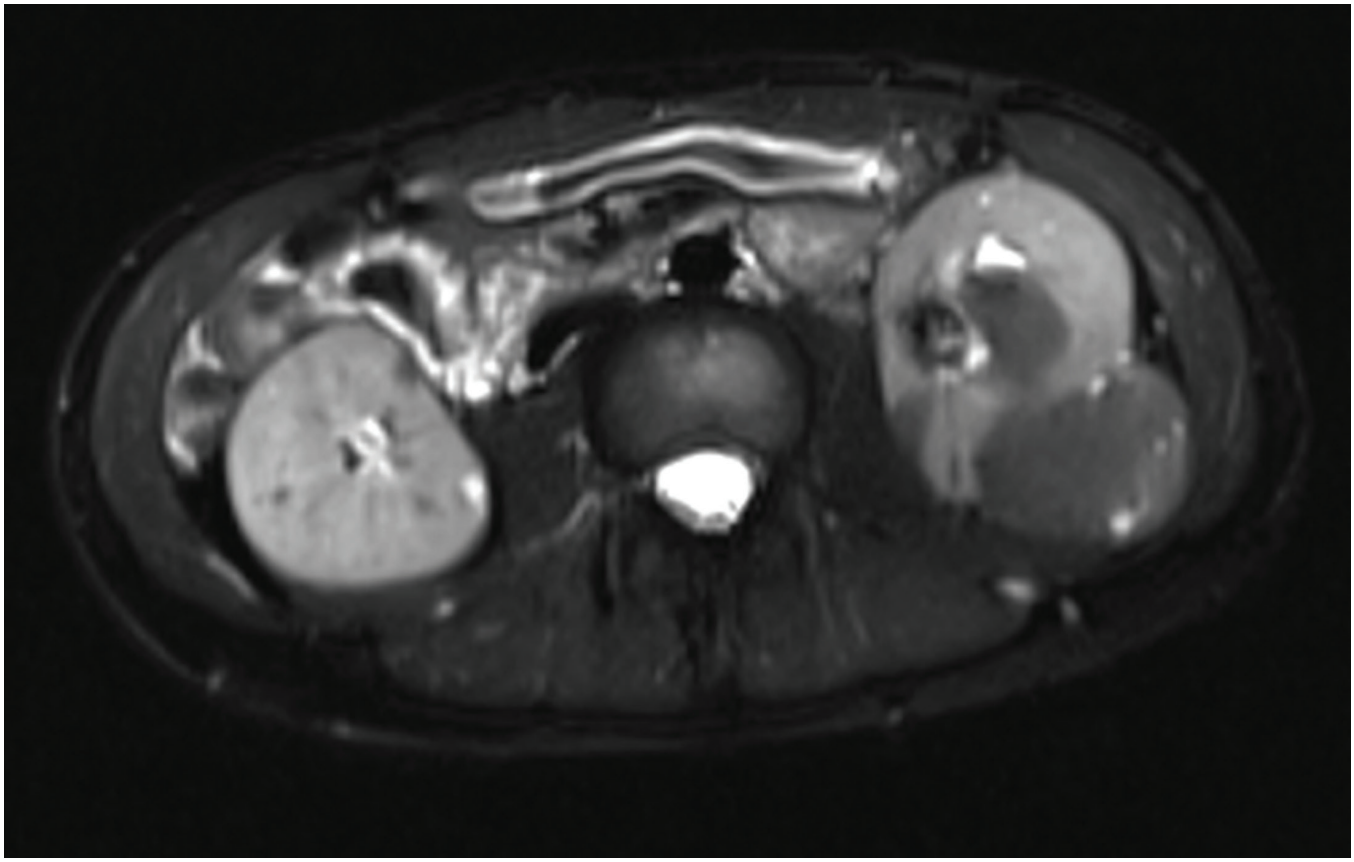

Figure 2. Exophytic fat-poor (atypical) AML in the left kidney of a TSC child (MRI)

Table 5. HT vs normotensive patients with TSC

	TSC children with HT	Non-HT TSC children	*P*
Number of patients (*n*)	7	48	-
Age (years)	8.9 ± 6.6	7.9 ± 4.3	0.588
Sex (boys/girls)	5 / 2	23 / 25	0.245
BMI (kg/m^2)	17.8 ± 2.8	17.8 ± 3.2	0.979
Schwartz GFR (mL/min/1,73 m^2)	110.0 ± 27.5	111.4 ± 15.4	0.844
Cholesterol (mg/dL)	163.7 ± 33.9	164.8 ± 34.9	0.939
Triglycerides (mg/dL)	111.6 ± 61.1	77.3 ± 32.5	0.026
Renal length (mm)	114.4 ± 21.8	92.4 ± 15.0	0.001
AML size (mm)	11.5 ± 7.5	13.2 ± 15.8	0.831
Cyst size (mm)	22.6 ± 27.1	6.3 ± 5.7	<0.001
TSC – tuberous sclerosis complex; HT – hypertension; *n* – number of patients; BMI – body mass index; GFR – glomerular filtration rate; AML – angiomyolipoma			

Table 6. Summary of clinical and biochemical data in four patients with contiguous gene syndrome (*TSC2/PKD1*)

Patient	Age (years)	Sex (M/F)	Schwartz GFR (mL/min/1.73 m^2)	HT (YES/NO)	Max cyst size (mm)
1	7.67	M	89.4	TAK	44
2	1.58	M	156.8	TAK	75
3	1.50	F	72.1	TAK	10
4	7.42	M	139.2	NIE	32
M – male; F – female; GFR – glomerular filtration rate					

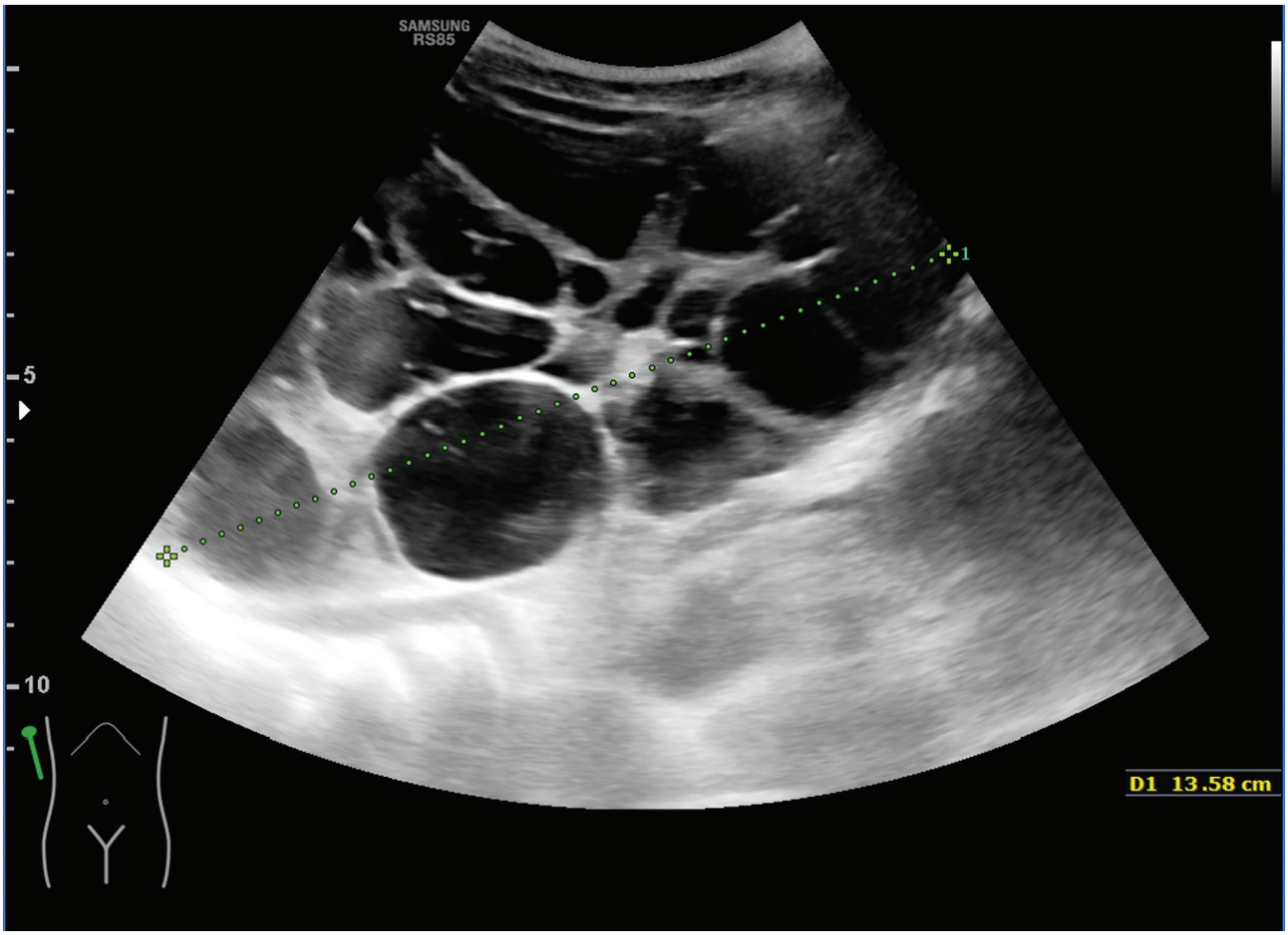

Figure 3. Cystic right kidney in a child with contiguous gene syndrome (TSC2/PKD1) (US)

possible progression to end-stage kidney disease in the second or third decade of life [18].

In our study group, HT was diagnosed in 7 of 55 patients (12.7%), including three CGS patients. The incidence of HT among TSC patients increases with age; according to the literature, it is observed in approximately 5% of children and 25% of adults [15, 16], although some data suggest that it may exceed 30% [19]. It is worth emphasizing that larger renal cyst size in our cohort was an HT risk factor, which lines with observations in children with autosomal dominant polycystic kidney disease (ADPKD) [20].

In the study group, nearly all patients had normal renal function, with the lowest GFR measured at 72 mL/min/1.73 m^2. GFR was assessed in our study using both the simplified Schwartz formula and the creatinine-cystatin C equation [11]. Cystatin C is recommended in patients with neurological disorders, including those with TSC. Such individuals may experience muscle atrophy, which can reduce creatinine production and lead to a falsely elevated GFR when estimated solely from creatinine [1]. It has been postulated that patients with TSC are at risk of hyperfiltration, attributed to overactivity of the mTOR pathway in the glomeruli, which may represent the earliest stage of kidney injury, analogous to diabetic kidney disease [19]. We also observed elevated GFR values in our cohort, including one child with PKDTS.

Elevated (abnormal) urinary albumin excretion was observed in 11 patients with TSC (20.0%). Albuminuria is an early and highly sensitive marker not only of impaired glomerular integrity but also of endothelial health throughout the body [14, 21]. It is important to emphasize that we demonstrated a positive correlation between AML size and the ACR index, indicating that renal parenchymal involvement by focal lesions is associated with an increased risk of CKD progression in these children [14].

As mentioned earlier, patients with TSC are at risk for the development and progression of chronic kidney disease. About 2–7.5% of TSC patients develop end-stage kidney disease, typically in adulthood, and at a significantly younger age in the case of those with PKDTS. Risk factors for end-stage kidney disease in TSC patients include the size and growth rate of renal lesions, prior surgical interventions (nephrectomy, embolization), and the presence of a co-occurring *PKD1* mutation [22].

In 2024, the European Reference Network for Rare Kidney Diseases (ERKNet) published updated recommendations for diagnosing and managing renal lesions in patients with TSC [23]. In the updated guidelines, as well as in the 2021 recommendations of the International Tuberous Sclerosis Complex Consensus Group, a growing AML >3 cm in diameter is an indication for initiating mTOR inhibitors (sirolimus or everolimus) [1, 23]. For diagnosed HT, first-line therapy consists of drugs to inhibit the renin–angiotensin–aldosterone system (RAAS) [23]. Fat-poor (atypical) AMLs pose a particular diagnostic and therapeutic challenge, as they may be mistaken for renal cancer on imaging studies. Renal cancer is characterized by a faster growth toward the renal hilum, whereas AML typically grows exophytically, outward from the organ [1]. In selected, uncertain cases, biopsy of the lesion may be considered [23].

In summary, it should be emphasized that clinically significant renal abnormalities occur already in children with TSC. The size of AMLs increases with age and correlates with urinary albumin excretion. Patients with CGS are a group with the most severe disease course and are at risk of developing end-stage renal disease already during childhood. Children with TSC require regular blood pressure measurements, evaluation of renal abnormalities through imaging, and monitoring of biochemical parameters in line with current recommendations. The specificity and interdisciplinary nature of the disease highlight the need for care provided by an experienced clinical team with access to advanced diagnostic and therapeutic modalities.

Conclusions

- Renal lesions are common in TSC children, with the most severe renal manifestations occurring in patients with contiguous gene syndromes.
- The size of AMLs in TSC children increases with age.
- Large AMLs are a risk factor for increased urinary albumin excretion in this patient group.
- In paediatric patients with TSC, large cyst size is a risk factor for HT.
- All paediatric patients with TSC should be followed up by a paediatric nephrologist.

Acknowledgements

We would like to thank Prof. Małgorzata Pańczyk-Tomaszewska and Prof. Sergiusz Jóźwiak for their support in implementing this project.

References

1. Northrup H, Aronow ME, Bebin EM, et al.; International Tuberous Sclerosis Complex Consensus Group. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol, 2021; 123: 50–66. doi: 10.1016/j.pediatrneurol.2021.07.011
2. Salussolia CL, Klonowska K, Kwiatkowski DJ, Sahin M. Genetic etiologies, diagnosis, and treatment of tuberous sclerosis complex. Annu Rev Genomics Hum Genet, 2019; 20: 217–240. doi: 10.1146/annurev-genom-083118-015354
3. Shepherd CW, Gomez MR, Lie JT, Crowson CS. Causes of death in patients with tuberous sclerosis. Mayo Clin Proc, 1991; 66: 792–796. doi: 10.1016/s0025-6196(12)61196-3
4. Kingswood JC, Belousova E, Benedik MP, et al. Renal angiomyolipoma in patients with tuberous sclerosis complex: findings from the TuberOus SClerosis registry to increase disease Awareness. Nephrol Dial Transplant, 2019; 34: 502–508. doi: 10.1093/ndt/gfy063
5. Bissler JJ,Christopher Kingswood J. Renal manifestation of tuberous sclerosis complex. Am J Med Genet C Semin Med Genet, 2018; 178: 338–347. doi: 10.1002/ajmg.c.31654
6. Thiravit S, Teerasamit W, Thiravit P. The different faces of renal angiomyolipomas on radiologic imaging: a pictorial review. Br J Radiol, 2018; 91: 20170533. doi: 10.1259/bjr.20170533

7. Kingswood JC, d'Augères GB, Belousova E, et al.; TOSCA consortium and TOSCA investigators. TuberOus SClerosis registry to increase disease Awareness (TOSCA) – baseline data on 2093 patients. Orphanet J Rare Dis, 2017; 12: 2. doi: 10.1186/s13023-016-0553-5
8. de Onis M. 4.1 The WHO Child Growth Standards. World Rev Nutr Diet, 2015; 113: 278–294. doi: 10.1159/000360352
9. Kułaga Z, Grajda A, Gurzkowska B, et al. Polish 2012 growth references for preschool children. Eur J Pediatr, 2013; 172: 753–761. doi: 10.1007/s00431-013-1954-2
10. Kułaga Z, Litwin M, Tkaczyk M, et al. Polish 2010 growth references for school-aged children and adolescents. Eur J Pediatr, 2011; 170: 599–609. doi: 10.1007/s00431-010-1329-x
11. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol, 2009; 20: 629–637. doi: 10.1681/ASN.2008030287
12. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med, 2008; 359: 1811–1821. doi: 10.1056/NEJMra0800885. Erratum in: N Engl J Med, 2010; 362: 2235
13. Stewart J, McCallin T, Martinez J, et al. Hyperlipidemia. Pediatr Rev, 2020; 41: 393–402. doi: 10.1542/pir.2019-0053
14. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int, 2024; 105: S117–s314. doi: 10.1016/j.kint.2023.10.018
15. Kingswood JC, Belousova E, Benedik MP, et al. Renal manifestations of tuberous sclerosis complex: key findings from the final analysis of the TOSCA study focussing mainly on renal angiomyolipomas. Front Neurol, 2020; 11: 972. doi: 10.3389/fneur.2020.00972
16. Eijkemans MJ, van der Wal W, Reijnders LJ, et al. Long-term Follow-up Assessing Renal Angiomyolipoma Treatment Patterns, Morbidity, and Mortality: An Observational Study in Tuberous Sclerosis Complex Patients in the Netherlands. Am J Kidney Dis, 2015; 66: 638–645. doi: 10.1053/j.ajkd.2015.05.016
17. Man A, Di Scipio M, Grewal S, et al. The genetics of tuberous sclerosis complex and related mTORopathies: current understanding and future directions. Genes (Basel), 2024; 15: 332. doi: 10.3390/genes15030332
18. Arredondo Montero J, Bronte Anaut M, Velayos M, et al. TSC2/PKD1 contiguous gene deletion syndrome. Clin Pediatr (Phila), 2024; 63: 411–413. doi: 10.1177/00099228231173911
19. Janssens P, Van Hoeve K, De Waele L, et al. Renal progression factors in young patients with tuberous sclerosis complex: a retrospective cohort study. Pediatr Nephrol, 2018; 33: 2085–2093. doi: 10.1007/s00467-018-4003-6
20. Massella L, Mekahli D, Paripović D, et al. Prevalence of hypertension in children with early-stage ADPKD. Clin J Am Soc Nephrol, 2018; 13: 874–883. doi: 10.2215/CJN.11401017
21. Viazzi F, Leoncini G, Conti N, et al. Microalbuminuria is a predictor of chronic renal insufficiency in patients without diabetes and with hypertension: the MAGIC study. Clin J Am Soc Nephrol, 2010; 5: 1099–1106. doi: 10.2215/CJN.07271009
22. Vabret E, Couchoud C, Lassalle M, Vigneau C. From tuberous sclerosis complex to end stage renal disease: who are these patients? J Nephrol, 2021; 34: 607–615. doi: 10.1007/s40620-020-00714-3
23. Mekahli D, Müller RU, Marlais M, et al. Clinical practice recommendations for kidney involvement in tuberous sclerosis complex: a consensus statement by the ERKNet Working Group for Autosomal Dominant Structural Kidney Disorders and the ERA Genes & Kidney Working Group. Nat Rev Nephrol, 2024; 20: 402–420. doi: 10.1038/s41581-024-00818-0