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Difficulties in the surgical treatment of patients with cystinuria – a case report

Trudności w leczeniu zabiegowym chorych z cystynurią – opis przypadku

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Abstract

Cystinuria is an autosomal recessive disorder. Two genes responsible for cystinuria have been identified: *SLC3A1* (chromosome 2p21) and *SL7A9* (chromosome 19q12). Their mutations cause high clinical variability in the course of the disorder. Over the past 10 years, an increase in the prevalence of cystinuria has been observed, which is now approximately 1:7,000 newborns. Similarly to cystic fibrosis, it is one of the most common diseases with this pattern of inheritance. Its clinical picture usually includes active stone formation (at least twice a year) and short periods of remission. Cystinuria relatively quickly leads to chronic renal failure. Patients with this disorder require constant supervision as well as monitoring of treatment outcomes. This paper presents a case of a 17-year-old boy diagnosed with cystinuria at the age of 3 months, when first bilateral pelvicalyceal stones were found on ultrasound. Immediately after the diagnosis, fluid supply was increased, treatment with captopril and a mixture of citrates (Shohl's solution) was initiated, which in later years was switched to potassium citrate/tiopronin. The implemented conservative treatment and constant nephrological care failed to prevent relapses in the patient. The boy underwent a total of 40 surgical interventions, including minimally invasive endoscopic procedures (extracorporeal lithotripsy, percutaneous nephrolithotripsy, ureteroscopic lithotripsy, retrograde intrarenal surgery) and three open surgeries to completely remove kidney stones.

Keywords: cystinuria, children, urolithiasis

Streszczenie

Cystynuria jest chorobą uwarunkowaną genetycznie, dziedziczoną w sposób autosomalny recesywny. Odpowiadają za nią dwa zidentyfikowane geny: *SLC3A1* (chromosom 2p21) i *SL7A9* (chromosom 19q12), a ich mutacje powodują dużą zmienność kliniczną przebiegu choroby. W ciągu ostatnich 10 lat zaobserwowano wzrost częstości występowania cystynurii, która wynosi obecnie około 1:7000 noworodków. Obok mukowiscydozy jest to jedna z najczęstszych chorób o tym typie dziedziczenia. Jej obraz kliniczny obejmuje zwykle aktywne powstawanie złogów (co najmniej 2 razy w ciągu roku) i krótkie okresy remisji. Cystynuria stosunkowo szybko doprowadza do przewlekłej niewydolności nerek. Pacjenci z tą chorobą wymagają stałego nadzoru, a także kontrolowania wyników leczenia. W niniejszej pracy przedstawiono przypadek 17-letniego chłopca, u którego w wieku 3 miesięcy rozpoznano cystynurię, a w badaniu ultrasonograficznym stwierdzono pierwsze złogi w układach kielichowo-miedniczkowych obu nerek. Bezpośrednio po ustaleniu rozpoznania zwiększono podaż płynów, rozpoczęto leczenie kaptoprilem i *mieszanką* cytrynianów (roztwór Shohla), które w latach późniejszych zamieniono na cytrynian potasu i tioproninę. Wdrożone leczenie zachowawcze i stała opieka nefrologiczna nie uchroniły pacjenta przed nawrotami choroby. U chorego wykonano łącznie 40 procedur zabiegowych, od małoinwazyjnych zabiegów endoskopowych (litotrypsja pozaustrojowa, przezskórna nefrolitotrypsja, litotrypsja ureteroskopowa, wsteczna chirurgia śródnerkowa), do konieczności trzykrotnego przeprowadzenia operacji otwartej, polegającej na całkowitym oczyszczeniu nerki z zalegających złogów.

Słowa kluczowe: cystynuria, dzieci, kamica układu moczowego

INTRODUCTION

Urolithiasis is the process of stone formation in the urinary tract. It occurs in about 1–20% of the population. Its prevalence depends on genetic and environmental factors[1]. Children account for 2–10% of all patients with urolithiasis. A sharp increase in the rates of urolithiasis, caused by changes in eating habits, high dietary sodium intake, obesity, type 2 diabetes, hypertension, and uncontrolled supply of multivitamins and dietary supplements, has been observed in developed countries[2]. Although a high-fibre diet reduces gastrointestinal calcium absorption, higher intake of protein increases excretion of uric acid, while an excess consumption of salt reduces the levels of crystallisation inhibitors, which promotes the formation of crystallization nuclei[2].

Children most often develop urolithiasis due to metabolic disorders. Inborn errors of metabolism often lead to the so-called active urolithiasis, i.e. formation of at least two stones per year as confirmed by imaging findings. In order to establish the aetiology of urolithiasis, tests are performed to determine the presence of serum and urinary electrolyte disturbances. The following serum parameters are assessed: blood count, urea and creatinine, calcium, uric acid, inorganic phosphates, magnesium, sodium, potassium, parathyroid hormone (PTH), thyroid stimulating hormone (TSH) and vitamin D ($1,25(OH)_2D_3$). A 24-hour urine collection is performed to assess the levels of calcium, phosphates, uric acid and cystine. These tests allow for the identification of the most common disorders such as hypercalciuria (increased calcium excretion), hyperoxaluria (increased oxalate excretion), hyperuricosuria (increased uric acid excretion), hypocitraturia (decreased citrate excretion), hypomagnesuria (magnesium ion levels below normal) and cystinuria (increased cystine excretion)[3].

Cystinuria is a rare yet important cause of kidney stones. It is an inherited defect in the resorption of cysteine and other amino acids, such as arginine, lysine and ornithine, in the proximal renal tubules. Although all of these amino acids are present at high levels in the urine, it is only in the case of cysteine that there is a risk of buildup in the urinary tract that persists throughout life, which is due to the low solubility of cystine in the urine. A low urinary pH promotes stone formation. The amino acid cysteine is found in large amounts in all proteins and, when degraded, it oxidises very rapidly to form cystine (two cysteines linked by a disulfide bridge). Cysteine plays a key role in heavy metal detoxification, protects against the harmful effects of alcohol and tobacco, and is essential for the synthesis of plasma proteins, creatine, glucagon and insulin[4].

Cystinuria is an autosomal recessive disease. Two genes responsible for cystinuria have been identified: *SLC3A1* (chromosome 2p21) and *SL7A9* (chromosome 19q12). Their mutations cause high clinical variability in the course of the disorder. Over the past 10 years, an increase in the prevalence of cystinuria has been observed, which is now approximately 1:7,000 newborns. Similarly to cystic fibrosis, it is one of the most common diseases with this pattern of inheritance.

Cystinuria accounts for about 1–2% of kidney stones in children. Normal 24-hour urinary cystine excretion is 70 mg/day; it exceeds 400 mg/day, and often reaches 1,300 mg cystine/1 g of creatinine in a 24-hour urine collection in children with cystinuria. An additional difficulty in assessing the amount of its excretion is the fact that the excretion of free cystine may be underestimated in patients with stones by its active deposition on the already existing concrements[5].

Although most patients with cystinuria develop stones in the first two decades of life, the clinical picture is highly variable. More than 80% of patients develop symptoms of the disease in the first years of life.

CASE REPORT

A 17-year-old boy has been under the care of the Department of Paediatric Surgery and Paediatric Urology of the Centre of Postgraduate Medical Education since the age of 4 years. He was born at 34 weeks gestation. Prenatal ultrasound (US) revealed only dilation of the right renal pelvis.

At the age of **3 months**, the boy was admitted to hospital due to a urinary tract infection, where diagnostic tests were run and bilateral nephrolithiasis was diagnosed. US findings for the left kidney were as follows: 1–2 mm stones in the calyces and 9 mm stones in the pelvis. In the right kidney, small 1–2 mm stones were found in the middle calyx and 2–3 mm stones were present in the inferior calyx. During hospital stay, cystinuria was suspected and it was recommended to maintain diuresis at around 600–800 mL/day, captopril at 1.75 mg/kg body weight, Shohl's solution 3 times a day (1 mL, 1 mL, 2 mL) and sulfamethoxazole at 30 mg/kg body weight + trimethoprim 6 mg/kg body weight in 2 doses per day.

At the age of **8 months**, the boy was again admitted to hospital due to a urinary tract infection. His body weight was 8,400 g. Urinalysis showed white blood cells densely covering the field of view; *E. coli* was obtained from urine cultures. US showed bilateral kidney stones – small bilateral deposits in calyces and a 9 mm stone in the left pelvis. During hospital stay, urine cystine was measured several times: 1,444, 1,545, 1,615 mg/g creatinine. The tests were also performed in the patient's family members: cystine was 177 mg/g creatinine in the mother, 265 mg/g creatinine in the father, and 281 mg/g creatinine in the grandmother (on the father's side). The 24-hour urine pH was also measured (during Shohl's solution administration) (Tab. 1). Based on the obtained results, recommendations for the patient were modified, increasing the dose of Shohl's solution up to 4 times a day (2 mL, 2 mL, 3 mL, 3 mL). The child remained under outpatient nephrological care.

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No.	Time	Urinary pH
1	10.30 a.m.	7.47
2	12.00 p.m.	7.01
3	12.25 p.m.	7.22
4	12.39 p.m.	7.30
5	02.05 p.m.	7.04
6	04.05 p.m.	7.62
7	05.15 p.m.	7.13
8	07.00 p.m.	7.49
9	09.00 p.m.	7.49
10	10.15 p.m.	6.88
11	02.00 a.m.	7.58

Tab. 1. 24-hour urine pH profile in the described patient at the age of 8 months

At the age of **2 years and 3 months**, the boy underwent a follow-up ultrasound, in which a 18 × 16 × 12 mm stone was found in the left kidney. Conservative treatment was continued, and less than a year later, when the patient was **3 years old**, an ultrasound scan showed that the stone in the left kidney had reached a size of 24 × 24 mm. The boy was qualified for extracorporeal shock wave lithotripsy (ESWL), which was performed three times with poor outcomes. After the procedures, the patient partially excreted the deposits, but subsequent follow-up ultrasound exams never showed their complete disintegration and evacuation.

At the age of **5 years**, the patient underwent computed tomography (CT) of the urinary tract and renoscintigraphy, and a cast deposit with a diameter of 4 cm was found in the left kidney. The function of the left kidney in renoscintigraphy was 43.77% of the effective renal plasma flow (ERPF; a parameter enabling the assessment of the involvement [%] of both kidneys in the clearance process). The boy was qualified for an open surgery – **pyelolithotomy with simultaneous endoscopic removal of stones from the renal calyces**. The procedure was uneventful. There were no residual deposits in the kidney after the surgery. Follow-up tests showed normal cystatin C levels and creatinine clearance.

At the age of **5 years and 8 months**, the boy was urgently readmitted to our hospital, where a bladder stone 40 × 20 mm in diameter, two ureteral stones 10–12 mm in diameter and a 20 mm renal pelvis stone were found. Endoscopic procedure was performed to remove the left-sided deposits in the upper urinary tract. Postoperative follow-up US showed only a 6–7 mm stone in the ureter. An analysis of the chemical composition of the largest stone showed 100% calcium oxalate.

At the age of **6 years**, the patient was urgently hospitalised in our department due to urinary retention. An 8 mm stone was impacted in the urethra, causing its complete obstruction. The deposit was crushed endoscopically and left for spontaneous evacuation.

In the years that followed, the boy was under nephrological care involving periodical check-ups. Among other things, the cyanide-nitroprusside test was performed to assess the 24-hour excretion of cystine and dibasic amino acids, and was positive. Additionally, potassium citrate at a dose of 2 × 1 tablet and thiopronine 5 × 1 100 mg tablet were included; however, stone formation was still observed. These deposits partially evacuated spontaneously (even those up to 9 mm in diameter) or as a result of procedures (two ESWL procedures and one ureterorenoscopic lithotripsy, URSL).

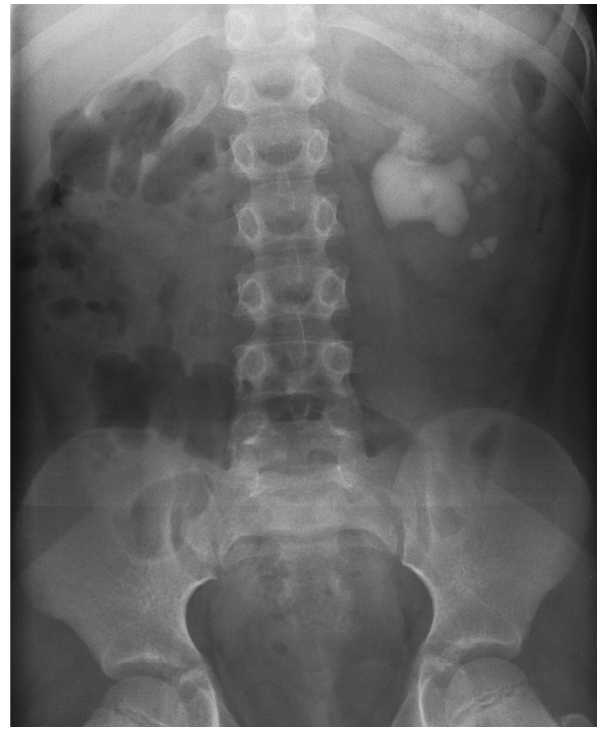

Fig. 1. Ultrasonography – a cast stone (diameter 42 mm) in the left kidney. The described patient was qualified for repeated pyelolithotomy with endoscopic removal of stones from the calyces

At the age of **9 years**, another follow-up US showed a cast deposit with a diameter of 42 mm in the left kidney (Fig. 1). The patient was qualified for another **pyelolithotomy with endoscopic stone removal**, and all deposits were removed during one surgery. After the procedure, no stones were found in imaging (Fig. 2). The first stone appeared 6 months later and again blocked the urethra. Emergency endoscopic urethrolithotripsy was performed, which allowed for complete stone fragmentation.

For the next 4 years, the boy was followed-up on an outpatient basis, undergoing periodical US, in which only small deposits that evacuated spontaneously were found. Parents confirmed that the child took all prescribed medications.

At the age of **14 years**, another US revealed a 36 × 18 mm stone with retention in the left kidney. A suspicion was raised based on urography (Fig. 3) that a subpelvic stenosis was caused by chronic inflammation of the urinary tract. The boy was qualified for **stone evacuation with simultaneous removal of the subpelvic stenosis**. All stones and stenoses were removed during the surgery. The procedure

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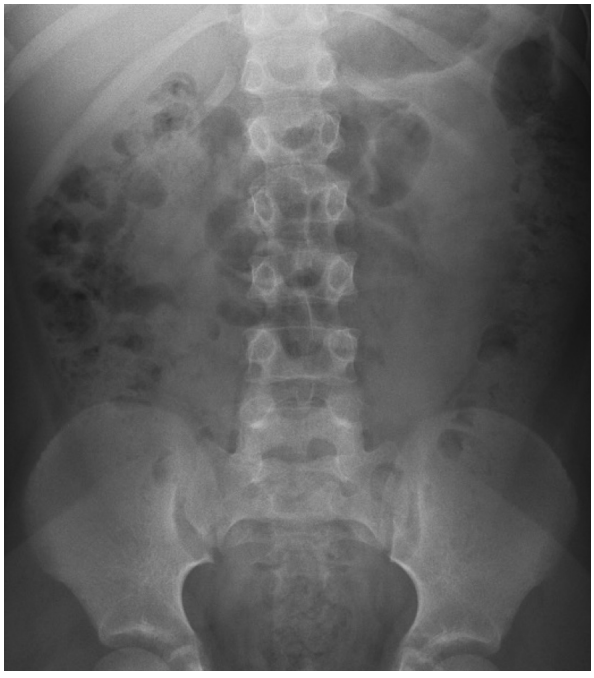

Fig. 2. A follow-up postoperative X-ray – the patient is free of stones

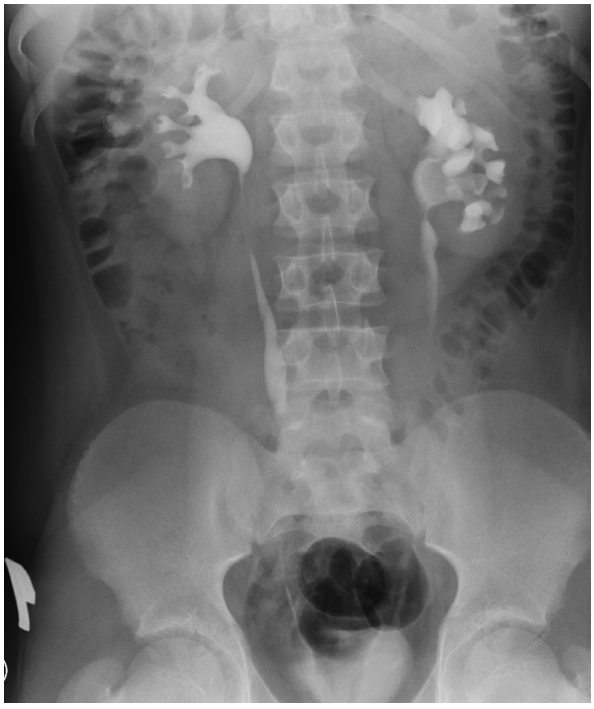

Fig. 3. Urography in the described patient – visible sub-pelvic stenosis on the left side

was complicated by a perirenal leak that resolved spontaneously. Six months later, US revealed the presence of small stones in the left kidney. The removal of the subpelvic stenosis made it possible to perform endoscopic procedures such as retrograde intrarenal surgery (RIRS). The ureter was prestented several times (Fig. 4). The prestenting procedure involves an insertion of a JJ catheter into the kidney

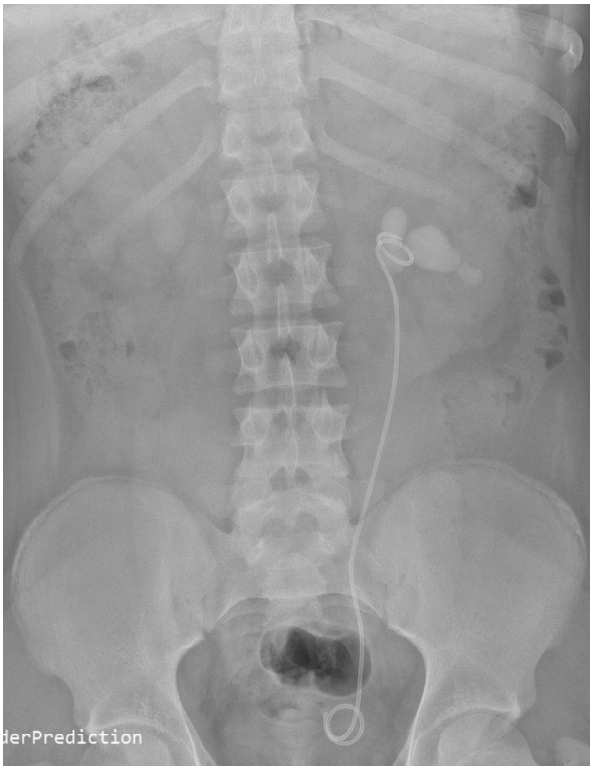

Fig. 4. An X-ray image – patient with a placed JJ catheter for pre-stenting before retrograde intrarenal surgery

for a period of about a month to dilate the ureter and allow for safer insertion of a flexible ureterorenoscope into the kidney. ESWL was performed several times with poor outcomes due to the hardness of cystine stones.

A follow-up dynamic scintigraphy revealed advanced post-inflammatory changes in the left kidney with a decrease in its clearance function (ERPF – 39%) and dilatation of the pelvicalyceal system without symptoms of impaired excretion. Also, slight post-inflammatory changes were described in the right kidney, but its secretory and excretory functions were normal (ERPF – 61%).

At the age of **16 years**, the boy was qualified for percutaneous nephrolithotripsy (PCNL), during which kidney stones were crushed using a high-power (120 W) holmium:YAG laser and evacuated through a nephrostomy (Fig. 5). PCNL was followed by three URSL procedures for renal colic and 3 ESWL procedures.

In the last few years, urine bacteriological tests have been repeatedly conducted due to stone colonisation by *Enterococcus faecalis*, *Escherichia coli*, *Stenotrophomonas maltophilia* and *Candida parapsilosis*. Treatment was based on an antibiogram.

At the age of **16.5 years**, the patient was admitted to hospital due to a complicated infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Chest CT showed ground-glass opacities, with 30–35% of lung parenchyma involved. The patient was treated with vancomycin and meropenem, oxygen therapy and heparin due to sub-segmental pulmonary embolism. He was additionally diagnosed with paediatric inflammatory multisystem syndrome (PIMS).

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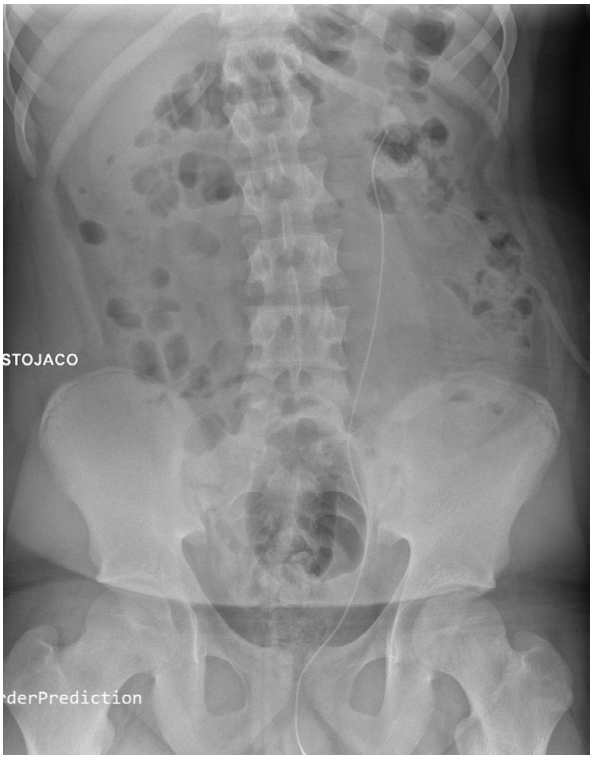

Fig. 5. An X-ray image – the patient after percutaneous nephrolithotripsy with visible nephrostomy and JJ catheter

Fig. 6. Avicenna Roboflex in the operating room

A robotic-assisted RIRS (Avicenna Roboflex robot, Fig. 6) was the last procedure so far performed in the patient. The boy was **17 years** old at that time.

A follow-up US performed in the 17-year-old patient showed a few small 1–2 mm stones in the left kidney. The follow-up period after the last treatment is 6 months (Fig. 7).

The boy had undergone a total of 40 surgical procedures to remove stones by the age of 17 years (Tab. 2). Unfortunately, the prognosis for further stone formation is not optimistic and further interventions may be needed.

DISCUSSION

Cystinuria is a rarely detected metabolic disorder caused by genetic mutations. The clinical picture of the disease is often varied. Unfortunately, the earlier its onset, the greater

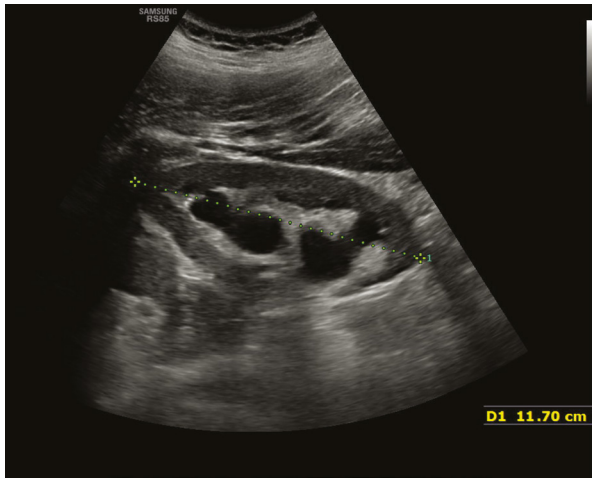

Fig. 7. Ultrasound after the last retrograde intrarenal surgery in the described patient

the tendency to form urinary tract stones and the worse the prognosis. Usually, stones in the upper urinary tract are the first symptom. They have specific shapes with smooth edges and a yellowish colour. The stones are very hard. Attempts to crush them with standard pneumatic probes are usually unsuccessful and high-power, high-frequency lasers are required. Most of the stones are formed of cystine, but a mixed composition can often be observed[6]. Larger stones cannot be crushed with the use of extracorporeal shock waves, as in the case of our patient. To achieve the desired effect, energy applied directly to the stone is needed. Therefore, minimally invasive procedures such as PCNL and RIRS are preferred in the surgical treatment of cystinuria. A high-power holmium:YAG laser can break the stone into fine particles. Unfortunately, cystinuria is recurrent in nature. The multiple interventions required to remove the stones lead to chronic renal failure. Treatment is aimed at arresting or slowing recurrent stone formation.

It is reported in the literature that chronic kidney disease (CKD) symptoms can be found in 50% of patients with cystinuria. Also, an increased prevalence of hypertension is observed in these patients. Only 25% of adult patients have a normal glomerular filtration rate (GFR) (>90 mL/min/1.75 m^2).

Early and correct diagnosis of cystinuria is essential to alleviate the course of the disease in the youngest patients[7]. Diagnosis enables early implementation of conservative treatment. Urine dilution, alkalisation, and chelation therapy are the mainstay of treatment. In asymptomatic periods, apart from typical pharmacotherapy used in cystinuria, general recommendations on proper fluid intake throughout the day should be implemented so that the specific gravity of the morning urine does not exceed 1.015 g/mL. A vegetarian, high-fibre diet, proper calcium intake (800–1,000 mg/day), limited consumption of methionine-containing products (meat and eggs) and salt are recommended. More intense physical activity and avoiding a sedentary lifestyle are also advised[8].

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No.	Type of procedure	Numbers of procedures
1	ESWL	17
2	URSL	7
3	RIRS	6
4	PCNL	1
5	Open surgery	3
6	Urethra – ureterolithotripsy	2
7	Prestaging the ureter as preparation for RIRS	4
	Total	40

ESWL – extracorporeal shock wave lithotripsy; **PCNL** – percutaneus litotrypsy; **RIRS** – retrograde intrarenal surgery; **URSL** – ureterorenoscopic lithotripsy.

Tab. 2. Number and type of procedures in the described patient

The use of minimally invasive procedures in the case of the need to remove stones allows to reduce the risk of damage to the renal parenchyma and extends the time of normal organ function, delaying the development of CKD[9,10].
Technological advances and miniaturisation of endoscopic equipment gave rise to a rapid progress in the treatment of urolithiasis. The use of minimally invasive techniques in surgery is particularly important in the case of cystinuria due to the high risk of recurrent stone formation. Stones usually fill the renal pelvis and at least a few calyces. In each case, the indications for a specific procedure should be considered in relation to its effectiveness, so that an optimal therapeutic approach can be selected.
RIRS, a highly specialised endoscopic technique that allows for an evaluation of the entire pelvicalyceal system to locate and crush the stones, and uses a high-power laser in direct contact with the stones, is an optimal method for stone evacuation in cystinuria. Avicenna Roboflex, the world's first robot for the treatment of urolithiasis, designed primarily for the RIRS procedure, is an additional surgeon's support, which enables safe, convenient, remote control of all available functions of flexible ureterorenoscopes. Precise laser fragmentation of large intrarenal stones allows for completeness of the procedure and ensures safety for paediatric patients. The robotic-assisted RIRS ensures higher effectiveness of stone removal, which is extremely important in the case of paediatric patients, as approximately 50–80% of them are projected to relapse. Reduced exposure to X-rays is an additional advantage of working with Avicenna Roboflex. The possibility to visualise the position and the degree of ureteroscope flexion allows to reduce the frequency of exposure to X-rays, which is of particular importance in the case of paediatric patients.

CONCLUSIONS

Cystinuria is a genetically determined disease in which stones are formed in the urinary tract. It requires a multidisciplinary collaboration of paediatricians, paediatric nephrologists, paediatric urologists, general practitioners and nutritionists. In the treatment of cystinuria, it is necessary to implement comprehensive prophylaxis and conservative management, with surgical treatment being a significant complement to the therapy aimed at preventing chronic kidney disease.

Conflict of interest

The authors do not claim any financial or personal relationships with other persons or organisations that could negatively influence the content of the publication and claim rights to this publication.

References

1. Kum F, Wong K, Game D et al.: Hypertension and renal impairment in patients with cystinuria: findings from a specialist cystinuria centre. Urolithiasis 2019; 47: 357–363.
2. Szmigielska A, Skrzypczyk P, Pańczyk-Tomaszewska M: Epidemiologia i rodzaje kamicy układu moczowego. Pediatr Med Rodz 2019; 15: 22–25.
3. Kamińska A, Bieroza I: Kamica układu moczowego u dzieci. Nowa Pediatr 2011; 2: 42–28.
4. Godziak A: Zastosowanie różnych technik analitycznych do badania oscylacyjnych wybranych aminokwasów białkowych. Praca doktorska. Instytut Chemii, Wydział Matematyki, Fizyki i Chemii, Uniwersytet Śląski Katowice 2017: 21–22.
5. Jobs K, Straż-Żebrowska E, Jung A: Trudności w diagnostyce i leczeniu pacjenta z odlewową kamicą układu moczowego w przebiegu cystynurii – opis przypadku. Pediatr Med Rodz 2011; 7: 253–256.
6. Eggermann T, Venghaus A, Zerres K: Cystynuria: an inborn cause of urolithiasis. Orphanet J Rare Dis 2012; 7: 19.
7. Rogowska-Kalisz A, Zeman K, Jaskólska E et al.: Skuteczne leczenie kamicy odlewowej (cystynowej) pęcherza moczowego u 2,5-rocznej dziewczynki – opis przypadku. Przegl Pediatr 2012; 42: 92–96.
8. Swatowski A: Leczenie zachowawcze kamicy moczowej. Forum Nefrol 2009; 2: 189–195.
9. Tiselius HG: New horizons in the management of patients with cystinuria. Curr Opin Urol 2010; 20: 169–173.
10. Rhodes HL, Yarram-Smith L, Rice SJ et al.: Clinical and genetic analysis of patients with cystinuria in the United Kingdom. Clin J Am Soc Nephrol 2015; 10: 1235–1245.

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