© Pediatr Med Rodz 2019, 15 (1), p. 33–37
DOI: 10.15557/PiMR.2019.0006

Received: 15.09.2018
Accepted: 06.11.2018
Published: 31.05.2019

Piotr Skrzypczyk, Małgorzata Pańczyk-Tomaszewska

Infectious urolithiasis

Kamica infekcyjna

Department of Paediatrics and Nephrology, Medical University of Warsaw, Warsaw, Poland
Correspondence: Piotr Skrzypczyk, Department of Paediatrics and Nephrology, Medical University of Warsaw, Żwirki i Wigury 63a, 02-091 Warsaw, Poland, tel.: +48 502 507 822, fax: +48 22 317 99 54, e-mail: pskrzypczyk@wum.edu.pl

Abstract

Infectious urolithiasis is a form of urolithiasis associated with the presence of bacteria in the urinary tract (*Proteus* spp., *Klebsiella* spp., *Providencia* spp., *Pseudomonas*, *Morganella morganii* and *Staphylococcus aureus*). These bacteria produce urease, i.e. an enzyme which decomposes urea. Deposits made of magnesium ammonium phosphate (struvite), sometimes combined with carbonate apatite, can quickly expand, fill the entire renal pelvis and lead to renal failure. In children, struvite urolithiasis has a variable frequency – in 1–29% of all patients with urinary tract deposits. The predisposing factors for the development of this urolithiasis in children are urinary tract defects and neurogenic bladder. Its symptoms are a combination of the symptoms of urolithiasis and urinary tract infection (fever, dysuria, lumbar pain, urinary urgency). In imaging studies, a large branched deposit is often visible, sometimes filling the entire renal pelvis and calyces. Treatment consists of surgical removal of deposits (most often by percutaneous nephrolithotomy) in combination with targeted antibiotic therapy. In Poland, combined treatment (percutaneous nephrolithotomy + ureterorenoscopy) proved to be a very effective and safe method, allowing the removal of large urinary deposits from the urinary tract in children. Antimicrobial treatment without surgical treatment is rarely effective. Other options for non-surgical management include reducing dietary phosphates, acidifying urine, administration of urease inhibitors (in adults) or citrates, and rinsing the renal pelvis with a solution of citrates or hemiacidrin. The prognosis in this group of patients depends mainly on the completeness of the surgical procedure and the lack of relapses.

Keywords: infectious urolithiasis, struvite urolithiasis, urinary tract infection, children

Streszczenie

Kamica infekcyjna to postać kamicy nerkowej związana z obecnością w drogach moczowych bakterii (*Proteus* spp., *Klebsiella* spp., *Providencia* spp., *Pseudomonas*, *Morganella morganii* oraz *Staphylococcus aureus*), które wytwarzają enzym ureazę – rozkładający mocznik. Złogi, zbudowane z fosforanu magnezowo-amonowego (struwit), czasami w połączeniu z węglanoapatytem, mogą szybko się powiększać, wypełniać całą miedniczkę nerkową i prowadzić do niewydolności nerek. U dzieci kamicę struwitową stwierdza się ze zmienną częstością – u 1–29% wszystkich pacjentów ze złogami w drogach moczowych. Czynnikami predysponującymi do rozwoju tej kamicy u dzieci są wady układu moczowego i pęcherz neurogenny. Jej objawy stanowią kompozycję objawów kamicy i zakażenia układu moczowego (gorączka, dyzuria, bóle w okolicy lędźwiowej, uczucie parcia na mocz). W badaniach obrazowych często uwidacznia się duży rozgałęziony złóg, niekiedy wypełniający całą miedniczkę nerkową i kielichy. Leczenie polega na zabiegowym usunięciu złogów (najczęściej metodą przezskórnej nefrolitotomii) w połączeniu z celowaną antybiotykoterapią. W doświadczeniach polskich kombinowane leczenie zabiegowe (przezskórna nefrolitotomia + ureterorenoskopia) okazało się bardzo skuteczną i bezpieczną metodą, pozwalającą na usunięcie dużych złogów infekcyjnych z dróg moczowych u dzieci. Leczenie przeciwdrobnoustrojowe bez zabiegowego rzadko jest skuteczne. Inne możliwości postępowania niezabiegowego obejmują ograniczenie fosforanów w diecie, zakwaszanie moczu, podawanie inhibitorów ureazy (u dorosłych) lub cytrynianów oraz płukanie miedniczki nerkowej roztworem cytrynianów lub hemiacydryny. Rokowanie w tej grupie chorych jest uzależnione przede wszystkim od doszczętności wykonanego zabiegu i braku nawrotów.

Słowa kluczowe: kamica infekcyjna, kamica struwitowa, zakażenie układu moczowego, dzieci

INTRODUCTION

Infectious urolithiasis (often identified with struvite urolithiasis) is a form of urolithiasis associated with the presence of urea-splitting bacteria in the urinary tract. Infectious deposits may grow very quickly (within a few weeks or months) and fill the entire renal pelvis, if proper treatment is not implemented. If not treated, infectious urolithiasis lead to kidney damage. In this disease, the treatment consists of surgical removal of deposits and a targeted antibiotic therapy.

PATHOGENESIS

The stones associated with the infection consist of magnesium ammonium phosphate ($MgNH_4PO_4$ – struvite), sometimes with the addition of carbonate apatite [$3Ca_3(PO_4)_2$*$CaCO_3$, another formula: $Ca_{10}(PO_4)_6CO_3$][1]. In healthy people, urine contains small amounts of these ingredients. Struvite stones are formed only in the case of increased production of ammonia (ammonium ion) and an increase in urinary pH, which reduces the solubility of phosphates. This is the case only in people with infection of the upper urinary tract with urease-producing bacteria, such as *Proteus* spp. (including *Proteus mirabilis*), *Klebsiella* spp., *Providencia* spp., *Pseudomonas*, *Morganella morganii* and *Staphylococcus aureus*[1–4].

The pathomechanism of the formation of infectious deposits is shown in Fig. 1. Urease decomposes urine present in urea to ammonia and carbon dioxide. It results in the increased availability of ammonia in the alkaline urine (often the pH of the urine exceeds the physiological values and reaches 8.5–9.0). This situation is different than in the case

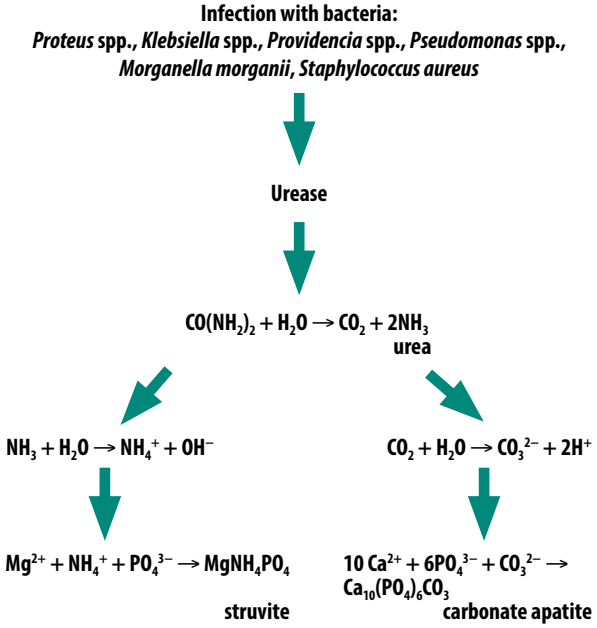

Fig. 1. Pathomechanism of the formation of infectious urolithiasis[4, own modification]

of clinical conditions in which ammonia is overproduced, but with simultaneous systemic acidosis and urine acidification (e.g. congenital metabolism defects – congenital hyperammonaemia). Ammonia produced in this reaction reacts with the water molecule to form an ammonium ion that is combined with magnesium and a phosphoric ion to form a struvite. At the same time, carbon dioxide forms carbonic acid. The dissociated bicarbonate anion is combined with calcium and phosphates and, as a result, carbonate apatite is formed. An important mechanism for the creation of struvite deposits is the destruction of glycosaminoglycans of the urinary tract lining by the produced ammonia. This makes it easier for bacteria to attach to the epithelium and create a biofilm[1,4].

The struvite deposit is actually a mixture of magnesium ammonium phosphate, protein matrix, leukocytes and bacteria. Formation of the deposit is a self-perpetuating process, as bacteria multiply in the stone. In addition, the presence of deposits in the urinary tract leads to urine retention, which causes further multiplication of bacteria, alkalisation of urine and deposition of subsequent portions of struvite. Struvite deposits can grow very large – they often fill the entire pelvis and calyces, which results in blocking the outflow of urine from the kidney[1,4].

A lot of patients suffer from mixed struvite and calcium oxalate urolithiasis. It is believed that in such situations, the calcium oxalate urolithiasis develops first, followed by bacterial superinfection and struvite deposits formation. In addition to infection, in such patients there is another congenital metabolic predisposition (hypercalciuria or hyperoxaluria)[5]. In the study of deposits containing struvite in Polish children, calcium oxalate, calcium phosphate and even uric acid admixtures were found[6].

Deposits (other than struvite and carbonate apatite) may also occur in the case of infection of the urinary tract with bacteria that do not have the ability to produce urease (e.g. *Escherichia coli*). In this situation, the infection may be secondary to the formation of deposits. It is also believed that these bacteria may predispose to the development of urolithiasis by inducing inflammation and by producing biofilms, which acts as a matrix for the growth of the deposit[7].

EPIDEMIOLOGY

The incidence of struvite urolithiasis in adults depends on their sex. It affects women three times as often because they have a greater risk of developing upper urinary tract infection. In the analysis of German data from the years 1977–2006, infectious urolithiasis was found in 3.8% of men and 11.0% of women with deposits in the urinary tract[8]. In children, this disease is diagnosed with a variable frequency: 1–29%[6,9–13] of all patients with urinary tract deposits. As in the case of adults, some studies indicate a higher incidence of struvite urolithiasis in girls[6,9]. It is more often found in younger children, which seems to be related to the prevalence of urinary tract infections

DOI: 10.15557/PiMR.2019.0006

and malformations in this group of patients[14]. Struvite urolithiasis may also occur in patients with other predisposing factors, such as neurogenic bladder or urinary system defects[15]. Urinary tract anomalies are found in one third of children with struvite urolithiasis[3]. Struvite and apatite urolithiasis of the urinary bladder are the most common forms of deposits in children with neurogenic bladder in whom clear intermittent catheterisation (CIC) is performed – including children after surgical augmentation of the neurogenic bladder[16,17] – as well as in patients with a urine reservoir prepared from the intestine[18]. In all of these cases, a chronic urinary bacterial infection is considered to be a causative agent.

In a study of 153 Polish children, struvite was a component of 33 (24%) of all deposits, and in 18 cases (13%), it was their main component. Out of 33 children with struvite, 13 had a urinary tract infection at the moment of diagnosis and another 17 had a history of infection; 10 patients had a neurogenic bladder[6].

In studies from China and India, low incidences of struvite (1.68% and 1.42%) and apatite (0.23% and 1.80%) stones were found. This may be due to the very frequent use of antibiotics in that part of the world[11,19].

Epidemiological studies indicate a decreasing frequency of infectious urolithiasis in children in the developed countries. This is due to the improvement of care, more effective treatment and prevention of urinary tract infections as well as more effective treatment of obstructive uropathy[20]. Also in adults in France, the incidence of infectious urolithiasis decreased – from 11.1% in the 1980s of the last century to 6.1% in the first decade of the 21st century[21].

SYMPTOMS

Symptoms of infectious urolithiasis are a composition of urolithiasis and a urinary tract infection (fever, dysuria, lumbar pain, urinary urgency). Common symptoms of renal colic are rare[4].

In the urinalysis, there is an alkaline pH and presence of nitrites and a positive reaction to leukocyte esterase, and in the sediment – apart from the features of infection (leukocyturia, sometimes leukocyte casts) – magnesium ammonium phosphate crystals. These crystals most often take the shape of the lid of the coffin, less often – a fern leaf[1,4,22]. In the urine culture, there is a significant colony count of bacteria that produce urease.

In imaging studies, a large branched deposit is often visible. If the appropriate treatment is not implemented, it fills the entire renal pelvis and calyces. The most accurate method for detecting struvite deposits is a computed tomography scan without contrast, which can depict deposits of even 1 mm in size. However, it has not been shown that it could accurately assess the composition of the detected deposit (including the presence of magnesium ammonium phosphate)[23].

The presence of magnesium ammonium phosphate in the deposit (obtained e.g. after surgical treatment) can be determined by means of infrared spectroscopy (a reference method)[24]. Other methods of the deposit composition analysis may falsely not show the presence of struvite. Therefore, with a typical clinical picture and risk factors, appropriate measures should be implemented even if no ammonium magnesium phosphate is detected.

TREATMENT

Due to the size of the deposit and the risks associated with it (sepsis, renal failure), patients – including paediatric patients – most often require surgical treatment combined with targeted antimicrobial therapy. Therapeutic options include: only pharmacological treatment, open surgery, laparoscopic surgery, percutaneous nephrolithotomy (PCNL), extracorporeal shock wave lithotripsy (ESWL), a combination of PCNL and ESWL treatments and a combination of PCNL and ureteroscopy[1,2,4].

Pharmacological treatment without surgical one is rarely effective. Microorganisms survive in the deposit, where antibiotic penetration is difficult, and create an alkaline environment that promotes the growth of the deposit. However, if positive urine culture is found, chronic targeted antibacterial treatment may be indicated to prevent further development of deposits[2]. It is recommended to take the culture not only from the urine, but also from the deposits obtained during the treatment[2,4].

Other possibilities for non-surgical management include reducing phosphate in the diet, acidifying urine, and administering urease inhibitors. Acidification of the urine (lowering the pH below 6.5) can be achieved by administering, for example, ascorbic acid, ammonium chloride or L-methionine[2]. At present, however, this procedure is extremely rare.

Currently, the only urease inhibitor used is acetohydroxamic acid (AHA; Lithostat). Urease inhibitors halve the risk of deposits growth[25]. Nevertheless, 20–60% of patients receiving AHA experience side effects such as palpitations, oedema, nausea, vomiting, diarrhoea, headache, dysgeusia, hallucinations, skin rashes, pains in abdomen and anaemia. These symptoms are reversible after discontinuation of the drug[4]. According to the American Urology Association (AUA), AHA can be used in adults in the absence of the possibility for surgical treatment or recurrent infectious urolithiasis[2]. Because of serious and frequent side effects, it is not recommended to give this medicine to children.

A non-standard method is irrigation (rinsing) of the renal pelvis with a 3.2% citrate solution (Renacidin) or 10% hemiacidrin solution (Suby's G solution)[4,26].

In preventing the formation of deposits or in inhibiting the growth of small residual deposits, the supply of potassium citrate may be effective. Chronic citrate therapy is recommended for patients who have residual deposits after 8 weeks after surgery[2]. There are no clear recommendations regarding the duration of chronic antimicrobial prophylaxis and preparations used.

 DOI: 10.15557/PiMR.2019.0006

Data on adults indicate mortality of up to 67% of patients who did not undergo surgery[27]. Therefore, conservative treatment alone is not recommended – with the exception of patients in severe condition.

Open surgical procedures are currently a rare method of treatment of struvite urolithiasis. They are performed in the case of the need to remove a non-functioning kidney, in the case of very large stones or in very obese patients[2,28]. According to AUA, PCNL is the best method to remove struvite deposits[2]. Its unquestionable advantages include: high efficiency in removing deposits, the possibility of direct assessment of the pelvis and calyces, the possibility to leave the drain and reassess the pelvis and calyces, speed of the procedure, and the ability to quickly assess its effectiveness[1,2,4]. In the case of PCNL procedures, the nephrostomy tube is routinely left, and the fragments of the deposit are removed through it.

AUA does not recommend performing only ESWL treatment in the treatment of struvite deposits – except for the patients with small stones and normal urinary tract anatomy. Its effectiveness is significantly lower compared to PCNL[2]. Sometimes combination of PCNL and ESWL techniques may be beneficial, especially in the case of large deposits or those whose fragments may not be available as part of the PCNL surgery. In such situations, the PCNL procedure is performed first, then ESWL, followed by another PCNL – to remove deposits crushed by the shockwave[2]. In order to ensure patency of the urinary tract in patients undergoing ESWL treatment, stenting (e.g. double-J catheter) is performed. Sometimes PCNL can be combined with ureterorenoscopy[2]. In the research by Jurkiewicz et al., such combined treatment (PCNL + ureterorenoscopy) proved to be a very effective method in children, which enabled the removal of large urinary tract deposits with simultaneous small side effects, and very good preservation of renal function[29]. The ureterorenoscopy procedure alone is not an effective treatment for struvite urolithiasis in adults and children[30].

The total incidence of surgical treatment complications is estimated at 13–19%, the least frequent being PCNL, more often at ESWL and open surgery[2].

Struvite urolithiasis is often found in children with congenital urinary tract malformations. It is then necessary to conduct a full diagnosis and, in justified cases, to implement the surgical treatment of a defect in order to prevent the recurrence of urolithiasis.

PROGNOSIS

Chronic infectious urolithiasis leads to recurrent pyelonephritis – with scarring of kidneys' parenchyma and progression to chronic kidney disease, and even to the end-stage renal failure. Data collected among adult patients from the Paris centre indicate that struvite urolithiasis, most frequently of all types of urolithiasis, leads to the end-stage renal failure[31]. In addition, bacterial inflammation may result in the onset of sepsis[2]. Spontaneous excretion of struvite deposits is extremely rare.

Prognosis in this group of patients is strictly dependent on complete removal of the deposit and lack of relapse. The percentage of patients free of relapse and infection reaches 90% if the stones are completely removed during the first treatment[1]. In the case of leaving a fragment of the deposit, the risk of recurrence of clinically evident urolithiasis ranges from 40% to 85%[1,2,4]. Patients with struvite stones require regular imaging (usually ultrasound imaging), because relapses are possible – also in the second kidney – especially in patients with risk factors for urinary tract infections. The necessity to perform a re-procedure (usually PCNL) varies from 10% to 40–50%[2].

Conflict of interest

Authors do not declare any financial or personal relations with other people or organisations which may negatively influence the content of this publication or claim the right to this publication.

References

1. Flannigan R, Choy WH, Chew B et al.: Renal struvite stones – pathogenesis, microbiology, and management strategies. Nat Rev Urol 2014; 11: 333–341.
2. Preminger GM, Assimos DG, Lingeman JE et al.: AUA Nephrolithiasis Guideline Panel. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. J Urol 2005; 173: 1991–2000.
3. Habbig S, Beck BB, Hoppe B: Nephrocalcinosis and urolithiasis in children. Kidney Int 2011; 80: 1278–1291.
4. Marien T, Miller NL: Treatment of the infected stone. Urol Clin North Am 2015; 42: 459–472.
5. Lingeman JE, Siegel YI, Steele BJ: Metabolic evaluation of infected renal lithiasis: clinical relevance. J Endourol 1995; 9: 51–54.
6. Kirejczyk JK, Porowski T, Filonowicz R et al.: An association between kidney stone composition and urinary metabolic disturbances in children. J Pediatr Urol 2014; 10: 130–135.
7. de Cógáin MR, Lieske JC, Vrtiska TJ et al.: Secondarily infected nonstruvite urolithiasis: a prospective evaluation. Urology 2014; 84: 1295–1300.
8. Knoll T, Schubert AB, Fahlenkamp D et al.: Urolithiasis through the ages: data on more than 200,000 urinary stone analyses. J Urol 2011; 185: 1304–1311.
9. Kamoun A, Daudon M, Abdelmoula J et al.: Urolithiasis in Tunisian children: a study of 120 cases based on stone composition. Pediatr Nephrol 1999; 13: 920–925.
10. Abhishek, Kumar J, Mandhani A et al.: Pediatric urolithiasis: experience from a tertiary referral center. J Pediatr Urol 2013; 9: 825–830.
11. Sun X, Shen L, Cong X et al.: Infrared spectroscopic analysis of urinary stones (including stones induced by melamine-contaminated milk powder) in 189 Chinese children. J Pediatr Surg 2011; 46: 723–728.
12. Coward RJM, Peters CJ, Duffy PG et al.: Epidemiology of paediatric renal stone disease in the UK. Arch Dis Child 2003; 88: 962–965.
13. Rellum DM, Feitz WF, van Herwaarden AE et al.: Pediatric urolithiasis in a non-endemic country: a single center experience from The Netherlands. J Pediatr Urol 2014; 10: 155–161.
14. Imran K, Zafar MN, Fatima N et al.: Chemical composition of stones in paediatric urolithiasis. J Ayub Med Coll Abbottabad 2017; 29: 630–634.

DOI: 10.15557/PiMR.2019.0006 PEDIATR MED RODZ Vol. 15 No. 1, p. 33–37

15. Kaefer M, Hendren WH, Bauer SB et al.: Reservoir calculi: a comparison of reservoirs constructed from stomach and other enteric segments. J Urol 1998; 160: 2187–2190.
16. Fontaine E, Gagnadoux MF, Niaudet P et al.: Renal transplantation in children with augmentation cystoplasty: long-term results. J Urol 1998; 159: 2110–2113.
17. Barroso U Jr, Jednak R, Fleming P et al.: Bladder calculi in children who perform clean intermittent catheterization. BJU Int 2000; 85: 879–884.
18. Helmy TA, Elawdy MM, AbdelHalim A et al.: Treatment of pouch stones after augmentation ileocystoplasty in children: is it always bothersome? Urology 2015; 85: 195–198.
19. Ansari MS, Gupta NP, Hemal AK et al.: Spectrum of stone composition: structural analysis of 1050 upper urinary tract calculi from northern India. Int J Urol 2005; 12: 12–16.
20. Lopez M, Hoppe B: History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol 2010; 25: 49–59.
21. Daudon M, Bouzidi H, Bazin D: Composition and morphology of phosphate stones and their relation with etiology. Urol Res 2010; 38: 459–467.
22. Cameron MA, Sakhaee K, Moe OW: Nephrolithiasis in children. Pediatr Nephrol 2005; 20: 1587–1592.
23. Marchini GS, Gebreselassie S, Liu X et al.: Absolute Hounsfield unit measurement on noncontrast computed tomography cannot accurately predict struvite stone composition. J Endourol 2013; 27: 162–167.
24. Krambeck AE, Khan NF, Jackson ME et al.: Inaccurate reporting of mineral composition by commercial stone analysis laboratories: implications for infection and metabolic stones. J Urol 2010; 184: 1543–1549.
25. Das P, Gupta G, Velu V et al.: Formation of struvite urinary stones and approaches towards the inhibition-a review. Biomed Pharmacother 2017; 96: 361–370.
26. Ferrandino MN, Monga M, Preminger GM: Adjuvant therapy after surgical stone management. Adv Chronic Kidney Dis 2009; 16: 52–59.
27. Teichman JM, Long RD, Hulbert JC: Long-term renal fate and prognosis after staghorn calculus management. J Urol 1995; 153: 1403–1407.
28. Honeck P, Wendt-Nordahl G, Krombach P et al.: Does open stone surgery still play a role in the treatment of urolithiasis? Data of a primary urolithiasis center. J Endourol 2009; 23: 1209–1212.
29. Jurkiewicz B, Zabkowski T, Jobs K et al.: Combined use of pyelolithotomy and endoscopy: an alternative surgical treatment for staghorn urolithiasis in children. Urol J 2016; 13: 2599–2604.
30. Dave S, Khoury AE, Braga L et al.: Single-institutional study on role of ureteroscopy and retrograde intrarenal surgery in treatment of pediatric renal calculi. Urology 2008; 72: 1018–1021.
31. Jungers P, Joly D, Barbey F et al.: ESRD caused by nephrolithiasis: prevalence, mechanisms, and prevention. Am J Kidney Dis 2004; 44: 799–805.