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Rare forms of nephrolithiasis

Rzadkie postacie kamicy nerkowej

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Abstract

Inborn errors of metabolism that may lead to calculus formation within the urinary tract include: adenine phosphoribosyltransferase deficiency, xanthine oxidase deficiency, orotic aciduria (acidosis) type I and alkaptonuria. All of them are autosomal recessive diseases. Adenine phosphoribosyltransferase deficiency and xanthine oxidase deficiency (congenital xanthinuria) are defects of purine metabolism, which lead to the formation of calculi composed of 2,8-dihydroxyadenine and xanthine. Xanthinuria is accompanied by hypouricaemia and hypouricosuria. Treatment involves a low-purine diet, abundant fluid administration and allopurinol (in adenine phosphoribosyltransferase deficiency) and alkalisation of urine (in xanthinuria). Orotic aciduria type I is a pyrimidine metabolism defect that manifests with failure to thrive, developmental delay, megaloblastic anaemia, immunodeficiency, skin appendage disorders and excessive excretion of orotic acid with urine. Nephrolithiasis is a rare manifestation of this disease. Treatment involves uridine and haematopoietic drugs. Alkaptonuria is a defect of tyrosine metabolism whereby homogentisate is deposited in tissues. It manifests with connective tissue pigmentation (ochronosis), osteoarthritis, calcifications in the coronary arteries, heart valve damage, pigmentation of the sclera and urolithiasis. Treatment involves nitisinone, vitamin C and dietary restriction of tyrosine and phenylalanine. Melamine urolithiasis is a consequence of crystallisation of melamine (cyanuramide), which was illegally added to infant formulas in China. Melamine stones were spontaneously evacuated from the urinary tract, but some patients developed irreversible renal changes. Moreover, certain drugs may also crystallise in the kidneys. These include aciclovir, indinavir, atanavir, sulphadiazine, triamterene, methotrexate, orlistat, ciprofloxacin and ceftriaxone. Prevention and treatment of this form of nephrolithiasis mostly consist in the administration of a large quantity of fluids.

Keywords: inborn errors of metabolism, melamine, drug-induced urolithiasis, children

Streszczenie

Wrodzone wady metabolizmu, które mogą prowadzić do powstania złogów w drogach moczowych, to: niedobór fosforybozylotransferazy adeninowej, niedobór oksydazy ksantynowej, acyduria (kwasica) orotowa typu I oraz alkaptonuria. Wszystkie te choroby dziedziczą się w sposób autosomalny recesywny. Niedobór fosforybozylotransferazy adeninowej i niedobór oksydazy ksantynowej (wrodzona ksantynuria) to defekty metabolizmu puryn prowadzące do tworzenia złogów, zbudowanych odpowiednio z 2,8-dihydroksyadeniny i ksantyny. W ksantynurii stwierdza się hipourikemię i hipourikozurię. W leczeniu stosuje się dietę niskopurynową, obfitą podaż płynów oraz allopurinol (w niedoborze fosforybozylotransferazy adeninowej) i alkalizację moczu (w ksantynurii). Acyduria orotowa typu I to wada metabolizmu pirymidyn objawiająca się niedoborem wzrostu, opóźnieniem rozwoju, anemią megaloblastyczną, niedoborem odporności, zaburzeniami przydatków skóry oraz nadmiernym wydalaniem z moczem kwasu orotowego. Kamica moczowa jest rzadką manifestacją choroby. Leczenie polega na podawaniu urydyny oraz preparatów krwiotwórczych. Alkaptonuria jest defektem metabolizmu tyrozyny, w którym dochodzi do odkładania homogentyzynianu w tkankach. Objawami są pigmentacja tkanki łącznej (ochronoza), zwyrodnienie stawów, zwapnienia w tętnicach wieńcowych, uszkodzenie zastawek serca, przebarwienia w twardówce oraz kamica moczowa. W leczeniu stosuje się nityzynon, witaminę C oraz ograniczenie w diecie tyrozyny i fenyloalaniny. Kamica melaminowa to efekt krystalizacji w drogach moczowych melaminy (cyjanuramidu), dodawanej w przeszłości nielegalnie w Chinach do mieszanek mlekozastępczych. Kamienie melaminowe ulegały spontanicznej ewakuacji z dróg moczowych, ale u części chorych doszło do nieodwracalnych zmian w nerkach. W drogach moczowych mogą krystalizować także niektóre leki (acyklowir, indynawir i atanawir, sulfadiazyna, triamteren, metotreksat, orlistat, cyprofloksacyna i ceftriakson). Profilaktyka i leczenie tej postaci kamicy polega przede wszystkim na podaży dużej ilości płynów.

Słowa kluczowe: wrodzone wady metabolizmu, melamina, kamica lekowa, dzieci

RARE FORMS OF UROLITHIASIS ASSOCIATED WITH INBORN ERRORS OF METABOLISM

There are several inborn errors of metabolism (IEM) that may lead to urolithiasis. These defects result in the accumulation of a poorly soluble organic compound that crystallises in the urinary tract. IEM causing specific types of calculi are[1]:

- adenine phosphoribosyltransferase deficiency;
- xanthine oxidase deficiency;
- orotic aciduria (acidosis) type I;
- alkaptonuria.

Adenine phosphoribosyltransferase (APRT) deficiency is an autosomal recessive error of purine metabolism that leads to the formation of 2,8-dihydroxyadenine crystals[2]. The literature reports ca. 300 patients with this disease and over 30 mutations in the *APRT* gene located on chromosome 16q24. The defect leads to the accumulation of adenine which is then metabolised by xanthine oxidase to 2,8-dihydroxyadenine[1]. The disease may be asymptomatic for many years, but may also manifest with urolithiasis in early childhood. Young children sometimes present reddish or brownish spots on diapers after voiding. Detection of 2,8-dihydroxyadenine (and distinguishing is from uric acid) is possible with sensitive tests, such as infrared spectrophotometry, mass spectrometry or X-ray crystallography[3]. The presence of the defect is confirmed through the evaluation of APRT enzyme activity in erythrocytes[4]. Treatment involves allopurinol to inhibit 2,8-dihydroxyadenine formation. Moreover, low-purine diet and abundant fluid administration are also instituted. This form of urolithiasis is not an indication to urine alkalisation as pH has no effect on the solubility of 2,8-dihydroxyadenine[3]. A delay in the diagnosis may result in progression to kidney failure.

Xanthine oxidase deficiency (also called congenital xanthinuria) is another autosomal recessive defect of purine metabolism. To date, 150 cases of this disease have been reported. Xanthine oxidase catalyses hypoxanthine conversion to xanthine and xanthine conversion to uric acid in the metabolism of purines[5]. There are two forms of this defect: isolated congenital xanthinuria (type 1, with urolithiasis) as well as xanthine oxidase deficiency concomitant with sulphite oxidase deficiency (type 2, with predominant neurological manifestations)[1]. The *XDH* gene coding xanthine oxidase is located on chromosome 2p22; only two pathogenic nonsense mutations are known. The absence of the enzyme (in congenital xanthinuria) results in no conversion of xanthine to uric acid, which produces hypouricaemia (uric acid concentration is usually below 1 mg/dL, i.e. below 59.5 µmol/L), hypouricosuria and excessive xanthine excretion with urine. Xanthine urolithiasis is present in one-third of the patients with type 1 congenital xanthinuria, whereas other patients remain asymptomatic[6]. To establish a diagnosis, it is necessary to test enzyme activity in intestinal or hepatic tissue[3]. Treatment consists in low-purine diet, administration of a large amount of fluids and alkalisation of urine (which slightly increases xanthine solubility)[3]. In some patients, accumulation of xanthine crystals in muscles leads to myopathy. Purine metabolism defects that may cause nephrolithiasis are presented in Fig. 1.

Orotic aciduria type I is an autosomal recessive inborn error of pyrimidine metabolism. Two types of this defect are distinguished: type I – deficiency of orotic acid phosphoribosyltransferase and orotidylic decarboxylase (orotidine 5'-phosphate), and type II – isolated deficiency of orotidylic decarboxylase. Urolithiasis occurs only in type I aciduria. Disorders are mostly caused by insufficient pyrimidine synthesis, imbalance of the purine–pyrimidine ratio and

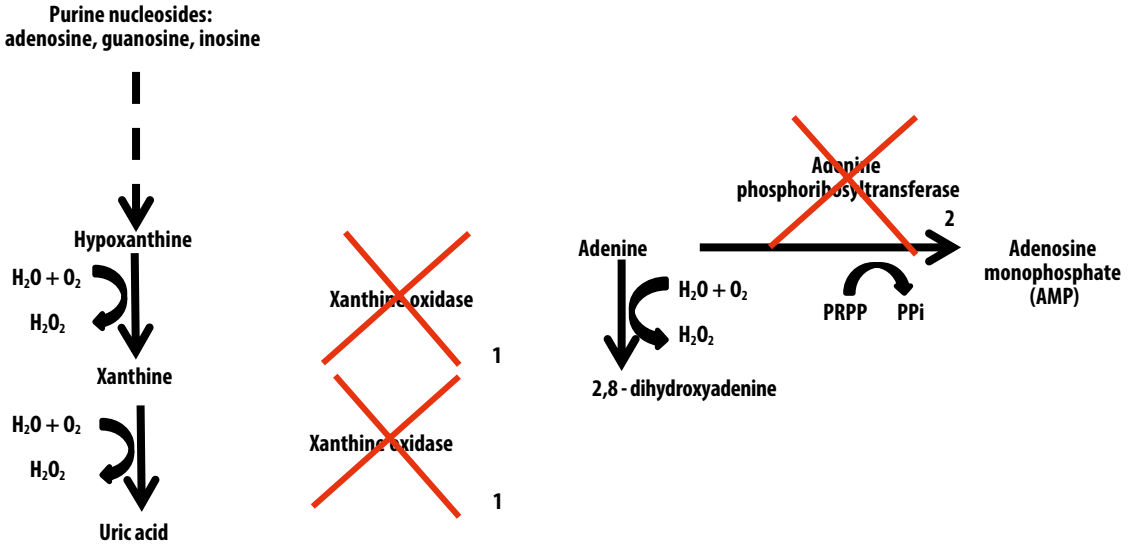

Fig. 1. Purine metabolism disorders leading to xanthine (1) and 2,8-dihydroxyadenine (2) urolithiasis[1, own modification]. PRPP – 5-phosphoribosyl 1-pyrophosphate, PPi – pyrophosphate

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nucleic acid deficiency[1]. Moreover, unused intermediate products accumulate and their toxic properties impair the central nervous system. Symptoms appear in early childhood (usually in the 3rd–7th month of life) and include: failure to thrive, developmental delay, megaloblastic anaemia, immunodeficiency, disorders of hair and nail growth as well as excessive excretion of orotic acid (a uridine metabolite), with urine[3]. Urolithiasis (orotic acid deposits) is a rare manifestation of this disease. Treatment of orotic aciduria consists in administration of uridine that may be a source of the remaining pyrimidines, which inhibits the synthesis of toxic intermediate products of the pyrimidine biosynthesis pathway. Moreover, haematopoietic products are supplemented. Metabolic disorders that lead to orotic aciduria are illustrated in Fig. 2.

Alkaptonuria is an autosomal recessive inborn error of tyrosine metabolism. The prevalence of the defect reaches 2–5 cases per 1 million. The defect is caused by deficiency of homogentisate 1,2-dioxygenase that catalyses the conversion of homogentisate to maleylacetoacetate[1]. When the enzyme lacks activity, homogentisate accumulates in tissues causing generalised connective tissue pigmentation (ochronosis), osteoarthritis (ochronotic arthropathy), calcifications in the coronary arteries, heart valve damage (mainly the aortic valve), pigmentation of the sclera (Osler's sign) and urolithiasis. Homogentisate, excreted with urine, is oxidised in the presence of oxygen to a brown or black pigment. The defect is usually associated with adult-onset urolithiasis, but the literature also contains isolated reports of nephrolithiasis in children[7]. An initial diagnosis can be established on the basis of the observation of urine reacting to bases (sodium or potassium hydroxide): it turns dark brown or black. The diagnosis is confirmed by the presence of homogentisic acid in urine. Genetic tests consist in the detection of given *HGD* mutations. Treatment involves high vitamin C doses and dietary restriction of tyrosine and phenylalanine. Moreover, patients are administered nitisinone which, when given regularly, may lower the homogentisate concentration by 95%[8]. Tyrosine and phenylalanine metabolism impairment that leads to alkaptonuria is presented in Fig. 3.

MALAMINE UROLITHIASIS

Melamine (cyanuramide, $C_3H_6N_6$) is a synthetic compound characterised by poor solubility in water (approximately 6 g/L in 37°C) and reacting with formaldehyde to form melamine formaldehyde resins. Melamine is used in industry and can be found in plastic dishes, car paints or glues. In September 2008, the Food and Drug Administration (FDA) and World Health Organization (WHO) informed about almost 300 thousand cases of renal diseases (nephrolithiasis, acute renal injury) in young children from China, caused by exposure to melamine added to infant formulas. Formulas with melamine have also been found in other countries (Japan, Taiwan, New Zealand, South Korea). An investigation conducted by the Chinese government has shown that 22 different companies added melamine to infant formula to falsify the amount of contained protein (a cross-reaction of nitrogen in melamine with nitrogen in protein)[9]. The analysis of calculi isolated from the affected children showed melamine and uric acid in equal molar amounts. It is suggested that melamine creates an insoluble complex with uric acid in urine[10]. A several-year observation of patients exposed to melamine in infancy indicates that calculi were spontaneously evacuated from the urinary tract, but some patients developed irreversible renal changes[11–13].

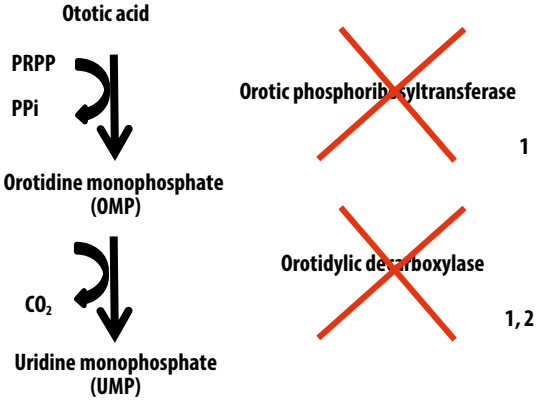

Fig. 2. Pyrimidine metabolism disorders leading to orotic acidosis: 1 – orotic aciduria type I; 2 – orotic aciduria type II[1, own modification]. PRPP – 5-phosphoribosyl 1-pyrophosphate, PPi – pyrophosphate

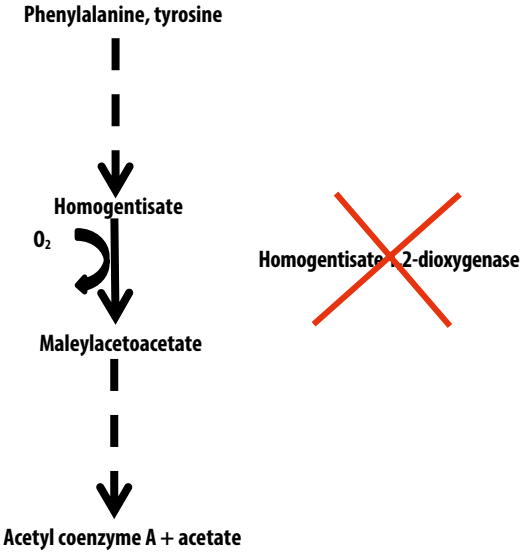

Fig. 3. Tyrosine and phenylalanine metabolism disorders leading to alkaptonuria[1, own modification]

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DRUG-INDUCED UROLITHIASIS

Drugs may also affect the risk of calculi formation, usually thought their influence on urinary excretion of lithogenic substances or inhibitors of stone formation (e.g. thiazide diuretics, carbonic anhydrase inhibitors). Certain drugs or toxins may also be substrates for the formation of calculus components (e.g. vitamin C and ethylene glycol – oxalates). Other drugs may crystallise in the urinary tract, thereby becoming a component of a calculus. They include: aciclovir, indinavir, atanavir, sulphadiazine, triamterene, methotrexate, orlistat, ciprofloxacin and ceftriaxone[14–17].

The possibility of drug crystallisation decreases with appropriate hydration. The risk should always be borne in mind if there are urolithiasis symptoms or if a stone is detected in imaging studies in patients exposed to these drugs[15].

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

References

1. Granner DK, Murray RK, Rodwell VW: Biochemia Harpera ilustrowana. Wydawnictwo Lekarskie PZWL, Warszawa 2018.
2. Edvardsson V, Palsson R, Olafsson I et al.: Clinical features and genotype of adenine phosphoribosyltransferase deficiency in Iceland. Am J Kidney Dis 2001; 38: 473–480.
3. Cochat P, Pichault V, Bacchetta J et al.: Nephrolithiasis related to inborn metabolic diseases. Pediatr Nephrol 2010; 25: 415–424.
4. Di Pietro V, Perruzza I, Amorini AM et al.: Clinical, biochemical and molecular diagnosis of a compound homozygote for the 254 bp deletion-8 bp insertion of the *APRT* gene suffering from severe renal failure. Clin Biochem 2007; 40: 73–80.
5. Akıncı N, Çakil A, Öner A: Classical xanthinuria: a rare cause of pediatric urolithiasis. Turk J Urol 2013; 39: 274–276.
6. Levartovsky D, Lagziel A, Sperling O et al.: *XDH* gene mutation is the underlying cause of classical xanthinuria: a second report. Kidney Int 2000; 57: 2215–2220.
7. Zibolen M, Srsnova K, Srsen S: Increased urolithiasis in patients with alkaptonuria in childhood. Clin Genet 2000; 58: 79–80.
8. Ranganath LR, Jarvis JC, Gallagher JA: Recent advances in management of alkaptonuria (invited review; best practice article). J Clin Pathol 2013; 66: 367–373.
9. Langman CB, Alon U, Ingelfinger J et al.: A position statement on kidney disease from powdered infant formula-based melamine exposure in Chinese infants. Pediatr Nephrol 2009; 24: 1263–1266.
10. Skinner CG, Thomas JD, Osterloh JD: Melamine toxicity. J Med Toxicol 2010; 6: 50–55.
11. Dai Q, Jiang Y, Tu W et al.: One-year follow-up of patients with melamine-induced urolithiasis in Southwest China. Int J Environ Health Res 2012; 22: 450–457.
12. Zou CC, Chen XY, Zhao ZY et al.: Outcome of children with melamine-induced urolithiasis: results of a two-year follow-up. Clin Toxicol (Phila) 2013; 51: 473–479.
13. Gao J, Wang F, Kuang X et al.: Assessment of chronic renal injury from melamine-associated pediatric urolithiasis: an eighteen-month prospective cohort study. Ann Saudi Med 2016; 36: 252–257.
14. Gagnon RF, Tsoukas CM, Watters AK: Light microscopy of indinavir urinary crystals. Ann Intern Med 1998; 128: 321.
15. Yarlagadda SG, Perazella MA: Drug-induced crystal nephropathy: an update. Expert Opin Drug Saf 2008; 7: 147–158.
16. Lafaurie M, De Sousa B, Ponscarme D et al.: Clinical features and risk factors for atazanavir (ATV)-associated urolithiasis: a case-control study. PLoS One 2014; 9: e112836.
17. Zhang Y, Ning B, Zhu H et al.: Characterizing ceftriaxone-induced urolithiasis and its associated acute kidney injury: an animal study and Chinese clinical systematic review. Int Urol Nephrol 2016; 48: 1061–1069.