

Hereditary Xanthinuria with Recurrent Urolithiasis Occurring in Infancy

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Abstract

Introduction: Hereditary xanthinuria, due to a purine metabolism disorder, is a rare cause of urinary lithiasis in children.

Case: We report the case of a three and half-year old child, who presented recurrent urinary lithiasis that, has led to the destruction of the right kidney. Infrared spectrophotometric analysis of the calculus showed that it was composed of 100% xanthine. Laboratory tests revealed hypouricemia and hypouricosuria with elevated urinary excretion of oxypurines. These findings led to a diagnosis of hereditary xanthinuria.

Conclusions: Early diagnosis of this rare disease is essential to avoid its complications. Metabolic causes must be sought in children with lithiasis.

Keywords: Hereditary xanthinuria; Urinary lithiasis

Introduction

Metabolic origin is a major cause of recurrent nephrolithiasis in children besides the other causes of urinary stones. Xanthine stones are associated with an excessive synthesis of purines or error of their metabolism. Clinical symptoms may include crystalluric urolithiasis and acute renal failure. In case unrecognized, xanthinuria can lead to nephrectomy or end-stage renal failure. We report a urolithiasis observation revealing a family xanthinuria.

Case Report

A 3-year-old boy was referred to the Department of Pediatrics for isolated abdominal pain, lasting for 15 days and being treated symptomatically without improvement. His clinical examination was normal. The plain abdominal X-ray showed the absence of radiopaque stones. Ultrasonography evaluation of the urinary tract showed a proximal ureteral stone of 8 mm of diameter with important distension of the intra-renal collecting system. The right renal parenchymal thickness was reduced and there was a compensatory hypertrophy of the left kidney. Cytobacteriological urinary analysis found 30,000 leukocytes/ml and a negative culture. A pyelolithotomy was carried out with removal of the stone. The immediate postoperative course was simple. One month later, ultrasonography revealed the recurrence of the ureteral lithiasis. An intravenous urography showed non-functioning of the right kidney until the 24th hour confirmed by the renal scintigraphy which also demonstrated a well-functioning of the left kidney.

During the surgery, ureteronephrectomy was performed because the right renal parenchyma was destroyed with coral lithiasis. Serum uric acid and urinary uric acid secretion was too low (Table 1). Crystalluria study showed a urinary pH at 6.02 and many atypical shaped crystals composed of polarizing granules. Atypical crystal of magnesium ammonium phosphate appeared after a 48 hour stay at 4°C. The sizes of the stone were 11 × 10 × 7 mm, and it was triangular shaped and salmon colored. Its surface was bumpy, rough and microcrystalline. The stone was of medium hardness and its section aspect was layered. The core was not individualized from the rest of the structure. The morphological analysis was unusual. However, the infra-red spectroscopy revealed pure xanthine content. Concentrations of serum oxypurines and urine hypoxanthine, determined using colorimetric methods and urine xanthine concentration, determined using gas chromatography were high. A family investigation was conducted and the results of blood and urine tests were collected (Table 2). The patient's father had a

	Serum		Urine	
	Results	Reference range	Results	Reference range
urea	7.9	1.8-6.4 mmol/L	625	430-710 mmol/24h
Creatinin	40	27-62 mmol/L	9.05	1.06-3.5 mmol/24h
Calcium	2.55	2.2-2.7 mmol/L	0.43	2.5-7.5 mmol/24h
Phosphorus	1.44	1.45-1.78 mmol/L	28.14	12.9-42 mmol/24h
Magnesium	1.01	0.7-0.95 mmol/L	2.7	3-5 mmol/24h
Uric acid	<5	120-320 mmol/L	0.17	1.48-4.43 mmol/24h

Table 1: Biological assessment of the patient.

	Serum			Urine		
	Uric acid (µmol/l)	Hypoxanthin (mmol/l)	Xanthin (mmol/l)	Uric acid (µmol/24h)	Hypoxanthin (mmol/l)	Xanthin (mmol/l)
The patient	<5	0.11	<0.01	0.17	0.79	0.89
The father	16	0.09	<0.01	0.104	0.50	0.69
The mother	250	-	-	6.509	-	-
The sister	208	-	-	3.761	-	-
Reference range	H: 150-420 F: 150-350	Undetectable	Undetectable	1.48-4.43	<0.20	<0.60

Table 2: Oxypurine profile of the family.

significant hypouricosuria and hypouricemia but serum oxypurines was elevated. Calcium oxalate crystals (mono- and dihydrate) were found in the urine. Serum uric acid levels in the patient's mother and sister were normal. Patient's mother urine showed an elevated uric acid level and calcium oxalate crystals dihydrate related to an insufficient urine dilution. Accordingly, we diagnosed hereditary xanthinuria, so, oral sodium bicarbonate, high fluid intake and low-purine diet were initiated. The outcome was favorable after a monitoring of 2 years.

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Discussion

For this patient, the infra-red spectroscopy revealed pure xanthine content referring to a hereditary xanthinuria. The diagnosis was confirmed by laboratory tests that showed a collapse of serum and urine uric acid with increased urinary excretion of oxypurines. Early diagnosis of this rare disease is crucial to avoid its complications. Hereditary xanthinuria, described in 1954 by Dent and Philpot, is a rare metabolic disorder with an incidence of 1/45 000 [1,2]. It is characterized by an absence of activity of xanthine oxidase or more exactly xanthine dehydrogenase. *In vivo*, the enzyme is present at xanthine dehydrogenase form and quickly converts into xanthine oxidase form *in vitro* [3]. This enzyme transforms hypoxanthine to xanthine and xanthine to uric acid. Enzyme deficiency causes an increase in the urinary excretion of oxypurines (xanthine and hypoxanthine), with a xanthine/hypoxanthine ratio of 4/1 [4].

Xanthine dehydrogenase deficiency may be isolated or associated with a deficiency of aldehyde oxidase, defining respectively the hereditary xanthinuria type I and II [5]. The gene encoding xanthine dehydrogenase is located on chromosome 2 [3,6,7]. The xanthinuria is transmitted as an autosomal recessive mode and two types of mutations have been described [8]. The disease is predominant in men and may occur at any age but rarely in children. Its distribution seems ubiquitous but more frequently in Asia and the Middle East [3]. Our case is the first reported in Tunisia. The xanthinuria is often latent, discovered incidentally by hyperuricemia or during a family survey. In fact, a high fluid intake and a low-purine diet can prevent stone formation. The disease is revealed by urinary calculi in 30-40% of cases [3,9]. The most frequent manifestations of urolithiasis in children are abdominal pain (44%), haematuria (38%), fever (15%) and other symptoms secondary to urinary tract infection [10]. Arthralgia, arthritis and myalgia were also described in hereditary xanthinuria [11,12]. These complications are explained by the low solubility of the xanthine causing precipitation of xanthine crystals in the kidneys, urinary tract, joints and muscles [3,6]. In our observation, crystals of magnesium ammonium phosphate discovered after storage at 4°C are due to secondary bacterial contamination because the urine collection was done in a collector in this young child who had no leukocyturia.

Xanthine stones are radiolucent and their morphology is round and brown. They are generally formed of pure xanthine; sometimes they are associated with hypoxanthine [6]. Uric acid stones and 2-8 dihydroxyadenine stones are also radiolucent so they are differential diagnosis with xanthine calculi. However, these two types of lithiasis are characterized by normal or elevated urinary uric acid secretion. Xanthinuria diagnosis is strongly suspected from the association of hypouricemia (<60 mmol/L), low urinary uric acid secretion (<0.5 mmol/24hours) and significant rise in the urinary elimination of oxypurines [3,7,13]. In healthy people, plasma oxypurines concentrations are undetectable. Its concentration exceeds 1 mg/L in homozygous Xanthinuria and may be normal in heterozygotes. In homozygous deficits, urinary elimination of oxypurines (normally <20 mg/24 hours) exceeds 300 mg/24 hours, with a xanthine/hypoxanthine ratio often >2 [6].

Oxypurines solubility in urine is pH-dependent and the xanthine

supersaturation at acid pH is constantly lithogenic [3,6]. The determination of xanthine oxidase activity confirms the diagnosis. This determination is made by biochemical, molecular or histological analysis, usually by duodenal biopsy or rarely by liver, kidney or skin biopsy [1-3]. The xanthine oxidase activity is near zero in homozygous and around 50% in heterozygotes [9]. The treatment of hereditary xanthinuria helps in preventing complications. It includes a high fluid intake (>3 liters/24 hour), alkalinization of the urine with monitoring of urine pH and a low-purine diet (eviction of offal, game, seafood, alcohol, chocolate and highly fermented cheese). Intense physical efforts promote intramuscular or kidney deposits of xanthine crystals so they are contraindicated. The treatment modality of xanthine stones depends on their size and location. Surgical stone removal should be reserved for urinary obstruction when lithotripsy has failed to relieve it [14]. Early diagnosis of this rare disease is essential to avoid its complications especially deterioration of renal function and urinary stones formation. Metabolic causes must usually be sought in children with lithiasis.

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