Classical xanthinuria: a rare cause of pediatric urolithiasis

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ABSTRACT

Xanthine dehydrogenase catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid in the final two steps of the purine degradation process. Xanthine oxidase deficiency is an uncommon cause of pediatric urinary stone formation, and classical xanthinuria. A ten-month-old boy presented with a seven-month history of nausea, vomiting, discomfort during urination, gross hematuria and passage of stones. His renal and liver function test results and electrolytes were within normal limits, but serum and urine uric acid levels were undetectable. Ultrasonographic evaluation of the urinary tract revealed the presence of multiple bilateral renal stones. Renal stones were analyzed using an X-ray diffractometer, and were found to be composed of hypoxanthine-xanthine. High fluid intake, alkalization and a low-purine diet were prescribed, and extracorporeal shock wave lithotripsy was performed. Recurrent renal stone formation was not observed during 18 months of follow-up. This case is reported to highlight the nature of this rare condition.

Key words: Urolithiasis; xanthinuria, xanthine dehydrogenase.

Introduction

Classical xanthinuria is an autosomal recessive hereditary disease which manifests as a result of deficiency of xanthine dehydrogenase which converts hypoxanthine, and xanthine into uric acid as the last step of purine metabolism. It is a very rare cause of pediatric urolithiasis. In classical xanthinuria urine, and blood uric acid levels drop, while hypoxanthine, and xanthine levels increase leading to urinary stones. It can manifest as a clinical picture starting from persistent complaints of vomiting, inability to gain weight, urinary system infections, and hematuria from birth progressing to chronic renal failure. We presented our case with the diagnosis of classical xanthinuria after informed consent of his parents was obtained so as to emphasize that early diagnosis, and treatment can prevent development of renal damage.

Case presentation

A ten-month-old pediatric patient was referred with symptoms of nervousness, crying during urination discoloration of urine, and stone fragments on his diaper. From his medical history, we learnt that he had symptoms of nervousness, and loss of appetite. He had been diagnosed as urinary tract infection one month

ago, and he had passed stone fragments 15 days ago, and used daily doses of 400 IU vitamin D. Her father, and mother were relatives. Any known family history of urolithiasis was not detected. On his physical examination his length, and weight were within 25. percentile. His systemic examination findings were unremarkable. Biochemical analysis revealed normal blood urea, creatinine, sodium, potassium, calcium, chloride, phosphorus, magnesium, protein, glucose, and blood gas levels, while uric acid level was too low (0.01 mg/dL, normal: 2.6-5.5 mg/dL). Urinalysis results were as follows: urine density 1020, pH 5.5, and microscopic erythrocyturia. Upright abdominal radiograms were unremarkable. On urinary system ultrasonograms (US), multiple renal stones (the largest ones being 12 mm in the right, and 14 mm in the left kidney) were seen. Daily metabolic urinalysis revealed normal calcium, magnesium, oxalate, citrate, cystine, but undetectable uric acid levels. Stone analysis by X-ray diffraction method in Tubitak Marmara Research Center identified the composition of the stone as hypoxanthine-xanthine (C₅H₄N₄O₂). With all these findings, the case was diagnosed as 'classical xanthinuria. Family screening tests did not disclose any evidence of urolithiasis in his parents, and two siblings. For the alkalization of

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urine, we started on potassium citrate therapy, besides diet with restricted purine content, and intake of abundant water were recommended. Extra-corporeal shock wave lithotripsy (ESWL) was performed, and stone-free state was achieved. During his 18 months of follow-up, urinary stone-disease did not recur, his height, and weight reached to 75. percentile.

Discussion

Classical xanthuria is the firstly described hereditary disorder of purine metabolism. However xanthine stone was originally reported in 1817 by Marcet. Its first clinical, and biochemical definitions were made in the years 1954, and 1959, respectively. Its enzymatic defect was originally determined in the year 1964.^[1,2]

In this autosomal recessive (AR) metabolic disease, two-thirds of these cases are of male gender. Its incidence ranges widely between 1/6000, and 1/69.000. In the literature less than 150 cases have been cited. Five cases have been reported from Turkey.^[2-5] The reported incidence rates of xanthine stones were 0.1, and 12% in Armenia (Arikyants, and Sarkissian), and Kuwait, respectively. which reveals that in countries where consanguineous marriages are more frequently encountered together with ethnic, and geographic differences, prevalence of xanthine stones increases.^[6-8] This patient was the first case of classical xanthuria diagnosed in our clinic.

Classical xanthinuria develops as a result of deficiency of xanthine dehydrogenase (XDH) which converts hypoxanthine, and xanthine into uric acid as the last step of purine metabolism.^[9] It has two types, Type I (OMIM 278300) occurs as an outcome of XHD-gene mutation on 2p22q chromosome. This gene has 36 exons, and encodes a polypeptide with 1333 amino acids.^[7] In Type II (OMIM 603592) xanthuria concurrent deficiencies of XHD, and aldehyde oxidase (AOX) are found. AOX gene is located on 2q33 locus.^[10] Clinically their manifestations are almost the same, and discrimination between these two types can be realized only with allopurinol loading test. Allopurinol is metabolized into oxypurinol with AOX enzyme.^[9] In Type I, oxypurinol is detected in blood, while in Type II it is not found. (Figure 1).^[11,12] Since follow-up, and treatment do not differ between both types, we didn't perform allopurinol test.

Most of the patients with classical xanthinuria are asymptomatic, and in 30% of the cases urolithiasis develops.^[1,9] Because of enzymatic deficiency, xanthine dehydrogenase can not be converted into uric acid which leads to increases in blood levels, and urinary excretion of hypoxanthine, and xanthine. Since these substances have a lower solubility in urine, they accumulate in the urinary system leading to formation of stones.^[11] Their symptoms can manifest from the neonatal period as persistent

vomitings, failure to gain weight, nervousness, urinary system infections, crystalluria, and hematuria. Its clinical course can progress from obstructive acute renal failure to chronic renal failure. Because of delayed diagnosis, and treatment, recurrent urinary tract infections, and staghorn stones, advanced renal damage necessitating nephrectomy can develop.^[6,7]

Excepting urolithiasis, myopathy (6.9%), recurrent polyarthritis (5.1%) can be seen. Its association with peptic ulcer has been reported.^[11] Age of onset of renal damage can change from pediatric age up to 80 years of age. However, more than 50% of them have been diagnosed before the age of 10.^[2] Relatives of the classical xanthinuria patients should be screened as for urolithiasis, and hypouricemia. In our case, our patient had symptoms of loss of appetite, failure to gain weight, and nervousness from 3 months of age. He had suffered from urinary tract infection, and had microscopic hematuria., Multiple renal stones were seen on urinary system sonograms. Family history did not disclose any evidence of urolithiasis or hypouricemia.

In classical xanthinuria, blood, and urine uric acid levels are very low (<2 mg/100 mL), and they can be easily detected.^[11] However, levels of hypoxanthine, and xanthine can be measured using high-performance liquid chromatographic (HPLC)

Figure 1. Discrimination between xanthinuria Types I (-), and II (=) in the xanthine –uric acid metabolic pathway

AMP: adenosine monophosphate; IMP: inosine monophosphate; GMP: Guanosine monophosphate; PRPP: 5-phosphoribosylpyrophosphate; ATP: adenosine triphosphate

methods employed for the detection of urinary, and blood amino acid levels.^[7] Normal values of xanthine, and hypoxanthine in 24-hour urine samples are below 40 mol/L, and 70 mol/L, respectively.^[11] Enzymatic deficiency can be demonstrated by measuring XDH levels in specimens harvested from duodenal mucosa or liver.^[6] Since it is an invasive procedure it is not used frequently for diagnostic purposes. Mutation analysis can be performed on DNA sequences isolated from peripheral blood leukocytes. However this procedure could be achieved in only scarce number of cases.^[3,7] Because of difficulties in performing other methods, use of X-ray diffraction method to demonstrate hypoxanthine-xanthine composition of the stone has a diagnostic value.^[2,3] In our case blood levels of xanthine-hypoxanthine were not measured. However, in the presence of hypouricemia, hypouricosuria, and non-opaque renal stone, demonstration of its xanthine-hypoxanthine content in stone analysis established the diagnosis of classical xanthinuria.

In the differential diagnosis of hyperuricemia, primary or secondary Fanconi syndrome, hereditary urate anion exchange transporter defect (URAT I) can be considered.^[7,12] Besides, Lesch-Nyhan syndrome with an increase in uric acid production can occur during allopurinol therapy.^[9] However, in these cases, stone analysis reveals the presence of uric acid, calcium oxalate, and phosphate in addition to xanthine. In our patient, clinical, and laboratory findings did not support these diagnoses.

It hasn't any specific medical treatment. Increased fluid intake, and diet with restricted purine content are recommended. Contrary opinions are prevalent on the treatment efficacy of alkalization of urine, and citrate therapy.^[9,11] Nina Arikyants et al.^[11] indicated that solubility of xanthine is not dependent on urine pH, and as a consequence alkalization therapy is ineffective.^[7,9] Treatment approach varies with the presence of stone size, and obstruction. We also initiated citrate therapy after ESWL, and during 18 months of the follow-up period, our patient benefited from alkalization, and urinary system stones did not recur.

In conclusion, less than 1% of cases with pediatric urolithiasis are xanthine-hypoxanthine stones. In cases of infantile urolithiasis with a family history of stone disease, metabolic causes should be investigated. In case of nonopaque stone, hypouricemia, and hypouricosuria, xanthinuria should be considered, and the presence of stone urinary system on US should be investigated. Using reliable methods like X-ray diffraction method, stone analysis should be done leading to early diagnosis. Thus with early diagnosis, and treatment renal damage can be prevented.

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