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Case report

First case of hereditary xanthinuria in a Moroccan family

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Abstract

The xanthinuria is a rare hereditary autosomal recessive disease. It is related to xanthine oxidase deficiency also known as xanthine dehydrogenase, an enzyme involved in the metabolism of purine bases. In this work, we describe the first cases of hereditary xanthinuria in a Moroccan family. We report a case of a 49-year-old woman, with type 2 diabetes, who was referred to the laboratory of clinical biochemistry for the first time for her periodic biological monitoring. In this patient, all measured biochemical parameters were normal except a moderate hyperglycemia and an undetectable uric acid in serum and urine. This prompted us to perform the assay of oxipurine in the urine. Urine samples from the younger brother and sister were also obtained and analyzed. High-performance-liquid-chromatography analysis showed an increase of urinary xanthine and hypoxanthine. The younger brother (43 years old), presented also an undetectable urinary uric acid. The determination of urinary oxipurines revealed an accumulation of xanthine and abnormal hypoxanthine concentration. Faced with these results, the diagnosis of hereditary xanthinuria was confirmed. It is a fortuitous discovery in this Moroccan family. The clinical examination did not find any signs described for this pathology such as myalgia or arthropathies. The presence of kidney stones has not been reported by abdominal ultrasound in our patients. The xanthinuria is a rare hereditary disorder. Xanthine oxidase deficiency is causing the accumulation of oxipurines whose major risk is the formation of xanthine calculi and progression to renal failure. Serious complications of this disease require early prevention by dietary measures in the absence of a specific treatment; so it is very important to detect the disease early, but it remains difficult because of the fact that this pathology is often asymptomatic.

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Introduction

Xanthinuria, which was first described in 1954 by Dent and Philpot [1], is a rare autosomal recessive disease. It is characterized by excretion of large amounts of xanthine in the urine and a tendency to form xanthine stones. Hereditary xanthinuria is a purine metabolism disorder due to inherited deficiency of the xanthine oxidoreductase (XOR) [2]. This enzyme catabolizes the oxidation of hypoxanthine to xanthine and xanthine to uric acid. Enzyme deficiency is the cause of an increase in the urinary excretion of xanthine and hypoxanthine, with a xanthine/hypoxanthine ratio of 4/1 [2,3]. Xanthine (oxydase) dehydrogenase deficiency can be isolated or associated with an aldehyde oxidase deficiency, defining respectively hereditary xanthinuria type I and II [4]. The human gene encoding for XOR is located at chromosome position 2p22, while that encoding aldehyde oxidase is at 2q33 [4-7]. Both types are characterised by plasma uric acid concentrations below 5mmol/l and plasma xanthine concentrations over 10mmol/l. Urinary excretion of uric acid is low or undetectable, and that of xanthine is high. Less than half of the affected people have symptoms, which are caused by deposition of xanthine in the urinary tract. This results in haematuria or renal colic and rarely in acute renal failure or chronic complications related to urolithiasis. Muscle pains caused by xanthine deposition occur in a minority of cases [5]. In this work we describe the first cases of hereditary xanthinuria in a Moroccan family.

Patient and observation

Case report: AS, a 49-year-old female from the center of Morocco, with type 2 diabetes, was directed to the laboratory of clinical biochemistry for the first time for her periodic biological monitoring. All measured biochemical parameters were normal except a moderate hyperglycemia and an undetectable serum uric acid (Table 1). The uric acid assay carried out on a second sample taken two months later gave the same result. The urinary uric acid was also undetectable. Faced with this major hypouricemia, we suspected a hereditary xanthinuria. Urine oxipurines, which were analysed by high-performance-liquid-chromatography (HPLC), revealed an increase of hypoxanthine and xanthine, together with a very low excretion of uric acid, thus confirming the diagnosis of hereditary xanthinuria (Figure 1, Table 2). Our patient was the eldest of a family of four children, born from non-consanguineous parents. Urine samples from the younger brother and sister were obtained. Urine uric acid and oxipurines were normal for the younger sister; however, the profile of the younger brother was typical of hereditary xanthinuria, with an accumulation of xanthine and normal hypoxanthine concentration (Figure 2, Table 3).

Clinically, the brother, who was 43 years old, did not show any sign of xanthinuria. The patient reported no history of kidney stones, no neurological and muscle signs and no arthritis symptoms. The clinical examination and psychomotor development were normal. The patient was then referred to the Nephrology Department. A radiographic assessment was performed in search of kidney stones including urinary tract without preparation (AUSP), renal ultrasound and pelvic CT scans. The radiography of the plain urinary tract did not objectify radiopaque urolithiasis (Figure 3). A complementary reno-bladder ultrasound showed a left calicielle dilatation without any identifiable obstacle (Figure 4). The CT urography (reno-bladder CT with contrast product injection) did not reveal any urinary calculus, but a dilated left calicielle, probably of hypotonic origin. For the younger brother, the radiological analysis was not performed because he did not turn up.

Biochemical analysis: uric acid in plasma and urine were measured using a specific enzymatic method adapted for an auto-analyzer (Cobas Integra 400 plus Analyzer, Roche). Oxipurines analysis was performed by high-performance-

liquid-chromatography coupled with a photodiode array detector (Waters, France) using a C18 column. The method allows the qualitative and quantitative determination of purine and pyrimidine bases. Molecules were identified by the analysis of the complete spectrum (190-320nm) and the comparison with reference spectra contained in the library and quantified at 254nm. This technique is applied to the analysis of purine and pyrimidine bases in plasma, cerebrospinal fluid (CSF) and urine.

Discussion

Here, we report the first cases of xanthinuria in a Moroccan family. The disorder was demonstrated by undetectable concentrations of uric acid in the serum and high excretion of xanthine in the urine. Both cases were clinically asymptomatic at the time of diagnosis of the pathology. Our patient presents an accumulation of xanthine and hypoxanthine with xanthine/hypoxanthine ratio superior to 3.5. While his brother presents an accumulation of xanthine and hypoxanthine, with a xanthine/hypoxanthine ratio that is more than 6.5. For our two patients, hereditary xanthinuria was confirmed, but we cannot determine whether it is type I or II because the allopurinol loading test was not done [8]. The radiological examination of our patient was normal except for a left calicielle dilatation without any identifiable obstacle. Six months after the diagnosis of hereditary xanthinuria, she had myalgias. These muscle pains worsened progressively and forced her to abandon her work as a housekeeper. Her diabetes was unbalanced with glycated hemoglobin up to 8% which constitutes a second risk factor predisposing to the development of renal failure. So far, about 150 patients with classical xanthinuria have been described worldwide [9]. The low concentration of uric acid in the serum and high excretion of xanthine in the urine can be used as a preliminary biochemical diagnostic marker of this disease. The xanthinuria is often latent and fortuitous discovery in front of a hypouricemia or during family screening are frequent [10,11]. In 30 to 40% of cases, the disease is revealed by urinary calculus [4,12,13] that can be prevented by a diet low in purines and animal protein with sufficient water intake. The more frequent clinical manifestations of urolithiasis in children are abdominal pain (44%), hematuria (38%), fever (15%) and other symptoms secondary to urinary tract infection [14]. Arthralgia, arthritis and myalgia were also described [11,15].

These complications are explained by the low solubility of xanthine causing precipitation of xanthine crystals in the kidney, the urinary tract, joints and muscles [4,6]. Xanthine dehydrogenase (XDH) deficiency can be isolated or associated with an aldehyde oxidase deficiency, defining respectively hereditary xanthinuria type I and II [3]. A clinically distinct third type of xanthinuria due to molybdenum cofactor deficiency is characterized by the lack of sulfite oxidase activity combined with xanthine dehydrogenase and aldehyde oxidase activities [9]. The types I and II of xanthinuria can be distinguished by allopurinol loading test. Since aldehyde oxidase converts allopurinol to oxipurinol, type II but not type I xanthinuria patients lack the ability to produce oxipurinol from allopurinol [8,16]. The determination of the activity of xanthine oxidase allows confirmation of the diagnosis. It is measured by biochemical, molecular or histological analysis, usually on duodenal biopsies, rarely liver, kidney or skin biopsies [11]. Molydenum cofactor deficiency can be identified by amino acids and oxipurines analysis and is biochemically characterized by low uric acid with high oxipurines and the presence of S-sulfocysteine with low 1/2 cystine. Hereditary xanthinuria is caused by mutations in genes xanthine dehydrogenase (XDH, 2p23.1) or in one of the genes involved in molybdenum cofactor biosynthesis (Mocos, 18q12.2). Xanthine oxidase provides other physiological functions. It is involved in iron absorption in the intestine and liberation of ferritin in the liver [17,18]. Stevens *et al.* [19] have demonstrated antimicrobial activity of xanthine oxidase in

maternal milk which contains a significant amount of this enzyme. It also has an inhibitory effect on viral growth [20].

Conclusion

In conclusion, we report two first cases of hereditary xanthinuria in a Moroccan family. In our patient the risk of developing renal failure is great, because of her unbalanced diabetes and the hereditary xanthinuria. The number of cases of hereditary xanthinuria declared worldwide is probably underestimated because of the fact that this pathology is often asymptomatic.

Competing interests

The authors declare no competing interests.

Authors' contributions

Aicha Ezoubeiri carried out the biochemical analyses and drafting of the manuscript. Asma Labaali conducted the survey with the family of the patient and the various radiological tests. Naima Fdil helped to write the manuscript and reviewed the literature. Jean-François Benoist performed the xanthine and hypoxanthine assays and participated in drafting of the manuscipt. Laila Chabaa conceived of the study, and participated in its design and coordination and helped to draft the manuscript.

Tables and figures

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Table 2: results of determination of urinary oxipurines of patient

Table 3: results of determination of urinary oxipurines of patient

Figure 1: corresponds to the chromatogram of the HPLC assay of urinary oxipurines of the patient. The peaks of hypoxanthine and xanthine are indicated by arrows respectively at 14.895 and 16.143 minutes

Figure 2: present the chromatogram of the HPLC assay of urinary oxipurines of the patient. The peaks of hypoxanthine and xanthine are indicated by arrows respectively at 14.483 and 15.821 minutes

Figure 3: corresponds to a radiological examination of the patient, radiography of the urinary tract without preparation, in order to search the presence of kidney stones, showing no radiopaque urinary stones

Figure 4: corresponds to a reno-bladder echography of patient in order to search the presence of kidney stones, showing a left calicielle dilatation indicated by arrows

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Table 1: results of standard laboratory tests of the patient

PARAMETERS	RESULTS	REFERENCE VALUES
Blood glucose	7 mmol/l	3,05-6,38 mmol/l
Serum urea	4,2 mmol/l	2,5-8,3 mmol/L
Serum Creatinine	89 µmol/l	44-106 µmol/L
Serum Calcium	2,48mmol/l	2,20-2,55 mmol/l
Serum Phosphorus	1,25mmol/l	0,87-1,45 mmol/l
Serum uric acid	Undetectable	142-339 µmol/L
Urine uric acid	Undetectable	2200-5475 µmol/L
Urine creatinine	9,1 mmol/l	2,55-20,0 mmol/l

Table 2: results of determination of urinary oxipurines of patient (A.S)

PARAMETERS	RESULTS	REFERENCE VALUES
Uric acid µmol/mmol creatinine)	Undetectable	<360
Xanthine µmol/mmol creatinine)	248	1-19
Hypoxanthine µmol/mmol creatinine)		

Table 3: results of determination of urinary oxipurines of patient (A.M)

PARAMETER	RESULTS	REFERENCE VALUES
uric acid (µmol/mmol creatinine)	**Undetectable**	< 340
Xanthine (µmol/mmol creatinine)	122	1-19
Hypoxanthine (µmol/mmol creatinine)	19	1-20

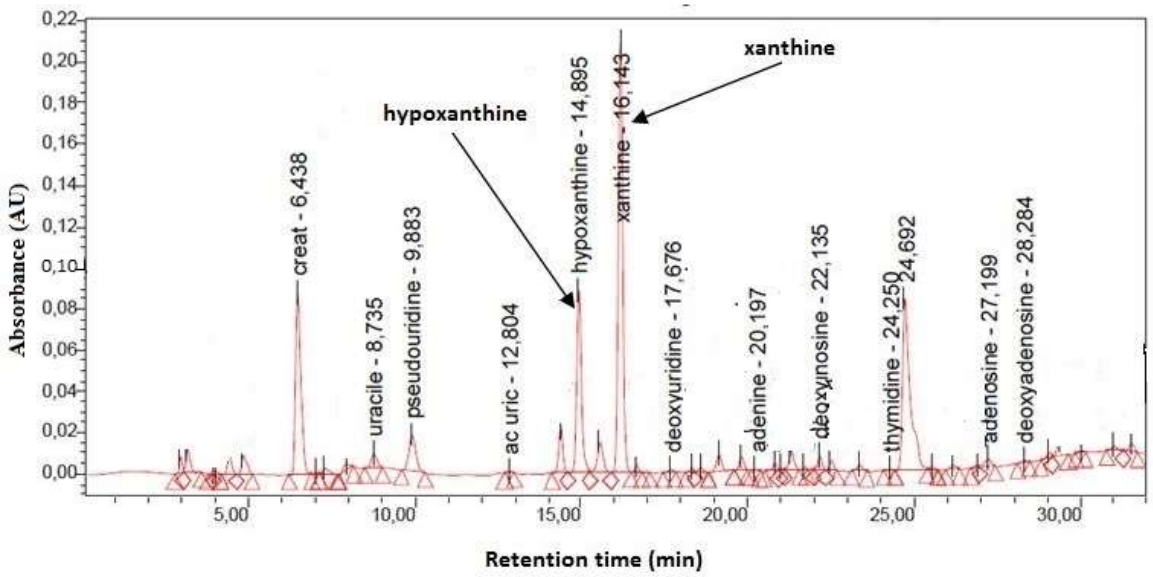

Figure 1: corresponds to the chromatogram of the HPLC assay of urinary oxipurines of the patient. The peaks of hypoxanthine and xanthine are indicated by arrows respectively at 14,895 and 16,143 minutes

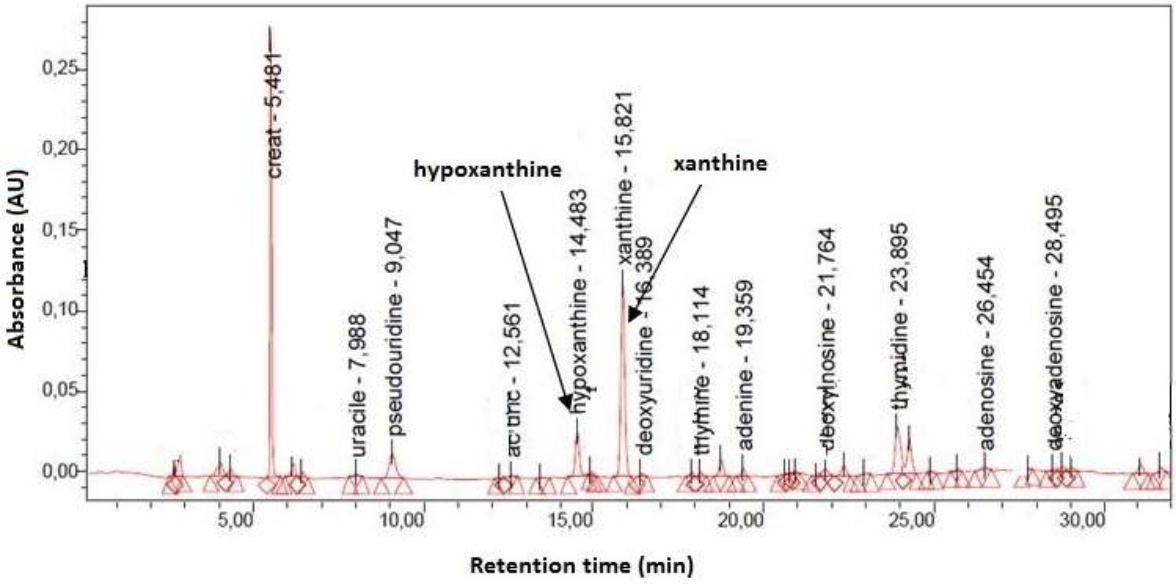

Figure 2: present the chromatogram of the HPLC assay of urinary oxipurines of the patient. The peaks of hypoxanthine and xanthine are indicated by arrows respectively at 14,483 and 15,821 minutes

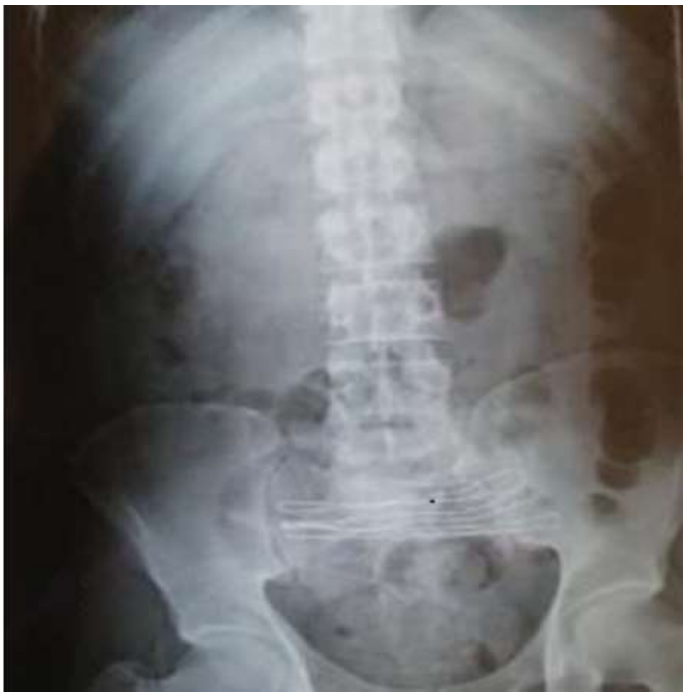

Figure 3: corresponds to a radiological examination of the patient, radiography of the urinary tract without preparation, in order to search the presence of kidney stones, showing no radiopaque urinary stones

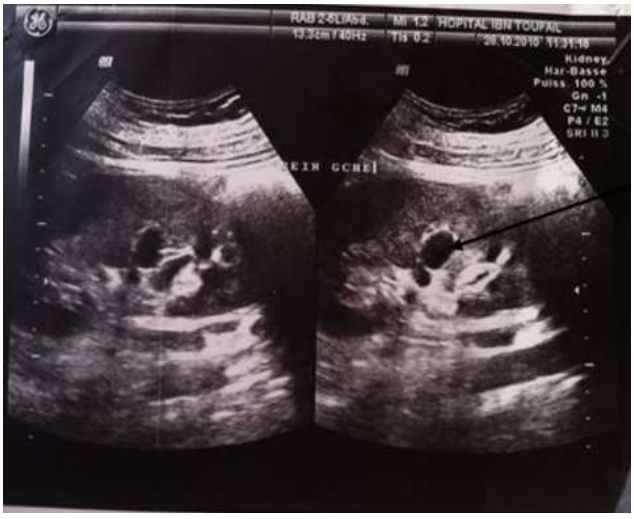

Figure 4: corresponds to a reno-bladder echography of patient, in order to search the presence of kidney stones, showing a left calicielle dilatation indicated by arrows