Hereditary xanthinuria

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Abstract
Xanthinuria is a rare autosomal recessive disorder associated with a deficiency in xanthine dehydrogenase (XDH - also referred to as xanthine oxidoreductase, XOR), which normally catalyses the conversion of hypoxanthine and xanthine to uric acid. In humans NAD+ is the electron acceptor and significant activity is confined to liver and intestinal mucosa. Irreversible conversion to oxidase occurs during ischaemia. The preferential accumulation/excretion of xanthine in plasma and urine results from extensive hypoxanthine recycling by the salvage pathway for which xanthine is not a substrate in humans: excess xanthine deriving from guanine via guanine deaminase. Classical xanthinuria has two types - an isolated deficiency (XDH type I), a dual deficiency with aldehyde oxidase (XDH/AOX: type II). Additionally xanthiuria occurs in Molybdenum cofactor deficiency, where sulphite oxidase (SO) is also inactive. More than 150 cases have been described from 22 countries, indicating that the disorder is not confined to specific ethnic groups. Although xanthinuria is a rare disorder the number of cases found is certainly an underestimate. Clinical symptoms in classical XDH deficiency include xanthine calculi, crystalluria, or acute renal failure and unrecognized can lead to end-stage renal disease, nephrectomy, or death. All symptoms relate to the extreme insolubility and high renal clearance of xanthine and can manifest from birth to the 80’s, 50% of cases being children. Duodenal ulcers, myopathy, or arthropathy have been noted in 10%. Treatment involves high fluid intake and dietary purine restriction. Twenty percent of type 1 and 2 patients (and occasional cofactor patients), have been asymptomatic.

Keywords
APRT: adenine phosphoribosyltransferase; AOX: aldehyde oxidase; 2,8-DHA: 2,8-dihydroxyadenine; SO: sulphite oxidase; XDH: xanthine dehydrogenase; XO: xanthine oxidase; RPLC: reversed phase liquid chromatography
Disease name and synonyms
Hereditary xanthinuria
Xanthine dehydrogenase (XDH) deficiency
Xanthine dehydrogenase (XDH: EC 1.2.1.37) normally catalyses the conversion of hypoxanthine and xanthine to uric acid. The enzyme was originally categorized as xanthine oxidase (XO:EC 1.2.3.2) but is really a dehydrogenase since in human tissue NAD+ is the electron acceptor. In humans significant XDH activity is confined to liver and intestinal mucosa [1]. Complete XDH deficiency leads to the replacement of uric acid in plasma and urine by xanthine, and to a lesser extent hypoxanthine. Hereditary xanthinuria was the first inherited purine disorder to be described, being recognized first as a clinical entity in 1954, xanthine stones having been identified over a century earlier [1]. The biochemical basis was established in 1959 and the enzyme defect confirmed in 1964., the two subtypes I and II of the classical defect being identified in 1990 [2].

Excluded diseases
The renal symptoms underline the need to add xanthine, as well as 2,8-dihydroxyadenine (2,8-DHA) lithiasis and uric acid lithiasis to the list of possible causes of persistent urinary tract infection, hematuria, urolithiasis, or acute renal failure in childhood. Because of the similarity in presentation, correct stone and metabolite identification is essential to exclude adenine phosphoribosyltransferase (APRT) or hypoxanthine guanine phosphoribosyltransferase (HPRT) deficiency and Phosphoribosylpyrophosphate synthetase (PRPS) superactivity, in all patients presenting with a history of crystalluria, urolithiasis and radiolucent stones [1]

Diagnosis criteria / definition
In classical xanthinuria plasma uric acid is low to absent, being replaced by xanthine in concentrations from 10 to 40 µmol/L with hypoxanthine concentrations of <5µmol/L. Xanthine is also the predominant purine excreted, with little to no uric acid. Because of its high renal clearance, urinary xanthine levels are generally well in excess of the solubility of xanthine in human urine, even at pH 7.0. In xanthinuric adults on a normal diet the mean urinary excretion ratio of xanthine to hypoxanthine is approximately 4:1 [1]. In healthy subjects with normal XDH activity, plasma concentrations of xanthine and hypoxanthine in blood and urine are low, irrespective of age or sex. The preferential accumulation/excretion of xanthine in plasma and urine results from extensive hypoxanthine recycling by the salvage pathway for which xanthine is not a substrate in humans; excess xanthine deriving from guanine via guanine deaminase. Diagnosis can be made from the near absence of uric acid in body fluids and its replacement predominantly by xanthine using a variety of techniques, but commonly by reversed-phase liquid chromatography (RPLC). However, bacterial infection can result in significant uric acid in the urine when measurement of plasma urate will be essential [1]. Confirmation of the enzyme defect is rarely made, since this involves invasive techniques such as intestinal or liver biopsy.

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Differential diagnosis
The two types of defect (I and II) identified, are clinically similar [2].
In the isolated Xanthinuria Type 1 defect patients lack only XDH activity, but have normal activities of AOX and SO. They can be distinguished in the laboratory by urinary screening. The evident inability to oxidize hypoxanthine and xanthine to uric acid is also identical in both defects, but substrates common to both XDH and AOX, such as allopurinol, are oxidized normally in type 1. The normal activity of SO is evident from the normal excretion of thiosulfate [1,4].
Xanthinuria Type II patients lacking both XDH and AOX, also have normal SO activity in that thiosulfate excretion is normal [1,4], but deficiency of AOX is evident from the inability to oxidize N-methyl nicotinamide to 2- and 4-pyridonecarboxamide or allopurinol to oxipurinol [2]. The mutation in Type II patients involving the common molybdenum cofactor sulphurase gene, which deletes the activity of XDH and AOX but leaves SO intact, has now been established [5].

Prevalence
More than 150 cases have been described from 22 countries [1,7], indicating that the disorder is not confined to specific ethnic groups: 47 cases (predominantly Type 1) were reported in Europe in a recent EC survey, compared with 82 for the cofactor deficiency [7]. Although xanthinuria is a rare disorder the number of cases found is certainly an underestimate, since, unless the presentation is associated with unusual features, cases are rarely published today. At least 20% have been totally asymptomatic sibs identified during the family studies. In 8% the defect has...
been benign and detected only during population studies, the remainder being detected by the finding of a very low plasma uric acid level during routine screening for a presumably unrelated disorder. From the limited data available the type 1 deficiency appears to predominate [7]. Xanthinuria is much more prevalent in the Mediterranean and Middle East than in Northern Europe, accounting for up to 12.9% of all kidney stones [9].

Clinical description
Symptoms which can be attributed directly to the defect - irritability, hematuria, urinary tract infection, renal colic, crystalluria, acute renal failure, or urolithiasis - have been reported in approximately 40% of patients. In some the full gamut of progression of renal disease leading to dialysis, transplantation and even death have been observed. Presentation after a bout of diarrhea, infection or vigorous exercise is common. Adults with the more serious renal complications frequently have a history of recurrent urolithiasis dating back to early childhood [1]. Duodenal ulcers, myopathy, or arthropathy have been noted in 10%. While uricosuria is the common presentation in childhood, muscle symptoms tend to develop later in life, supporting the concept that tissue oxypurines may take time to reach critical levels.

Management including treatment
Because of the poor solubility of xanthine at any pH, alkalisation of the urine is relatively ineffective and a high fluid intake, where possible, coupled with a diet low in purines is the only therapy for classical xanthinuria. Vigorous exercise and extremely warm climates should be avoided XDH is much more frequent around the Mediterranean than in Northern Europe. In many patients the disease has been severe enough to require lithotomy. More recently, therapy using extracorporeal shock wave lithotripsy with sonographic stone localization has proved beneficial [1].

Diagnostic methods
Both the classic and the combined defects may be identified by the finding of low to undetectable levels of uric acid in plasma and/or urine, together with the specific metabolites xanthine and hypoxanthine which replace uric acid in the defect. Measurement of urinary uric acid is essential because, as demonstrated by several different surveys, hypouricemia can result from a variety of other causes, both inherited or acquired [1]. Numerous sensitive methods for identifying hypoxanthine and xanthine in both plasma and urine by conventional spectrophotometry, chromatography, capillary electrophoresis or RPLC exist [10].

Etiology
The clinical consequences in classical xanthinuria relate to the extreme insolubility of xanthine in urine at any pH. Unlike uric acid, the solubility of xanthine at pH 5.0 (0.5 mmol/L) is not greatly enhanced by alkalisation of the urine (0.9 mmol/L at pH 7.0), which presents problems for treatment [1]. The potential toxicity of xanthine in humans relates to the high renal clearance. Consequently, the risk of precipitation in the kidney or urinary tract is high, particularly in an infant with a history of vomiting, diarrhea or recurrent infection and can lead to eventual tubular blockage and acute renal failure. In some patients the renal damage has led to clubbing of the calyces of the kidney, hydronephrosis, chronic renal failure and nephrectomy. Plasma xanthine concentrations up to 243µmol/L were found in an adult patient in terminal uremia. The potential nephrotoxicity of xanthine in humans is supported by studies in pigs fed guanine together with allopurinol, which precipitated acute renal failure [6]. Crystalline deposits of xanthine in the distal tubules produced extensive tubular epithelial damage, interstitial edema and inflammation leading in the long-term to shrunken kidneys with severe and permanent renal damage.

Xanthinuria, can occur secondary to therapy with allopurinol in situations associated with endogenous uric acid overproduction. Patients with the Lesch-Nyhan syndrome, or partial HPRT deficiency, show a rapid rise in xanthine following allopurinol and have presented with xanthine stones, or evidence consistent with xanthine nephropathy. Renal sonography of Lesch-Nyhan patients on long-standing treatment has shown variable ultrasonic appearances of multiple calculi and increased medullary echogenicity in some [1]. Grossly elevated plasma xanthine (600-700 µmol/L), together with urinary concentrations of nearly 1mmol/L creatinine (instead of the normal <0.01 mmol/L), have also been noted in patients developing acute renal failure when given allopurinol concomitantly to prevent uric acid nephropathy during aggressive therapy for different malignancies [1]. Treatment should be carefully monitored to ensure a reasonable balance is achieved between xanthine and uric acid.
duodenal or jejunal mucosa biopsy. Liver biopsies have been performed only when there were other indications.

**Genetic counseling**
Not appropriate except for the cofactor deficiency

**Antenatal diagnosis**
Not appropriate for XDH types I and II, but available for the cofactor deficiency [8].

**Unresolved questions**
Whether XDH, because of its localization exclusively in liver and intestinal mucosa in humans really has a role in ischaemia-reperfusion damage in humans [1].

**References**

http://www.orpha.net/data/patho/GB/uk-XDH.pdf