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Litiasis due to 2,8-dihydroxyadenine, usefulness of the genetic study☆

Litiasis por 2,8-dihidroxiadenina, utilidad del estudio genético

Dear Editor,

Renal lithiasis affects 6–15% of the western population,[1] and the causes are usually being well identified. However, in some cases the diagnosis is more complex and the rapidity of the diagnosis has important consequences in the prognosis. We present one example of this here.

The patient was a 27-year-old male who was referred to our clinic from the primary care physician with haematuria. His previous medical history included allergy to aspirin, appendectomy and he was an active smoker. At the age of 13, he had macroscopic haematuria (seen in another hospital), and was diagnosed with haematuria secondary to exercise. At 23, he had a lower urinary tract infection, which was treated conventionally. At 24, he suffered a first episode of expulsive renal stone, with another episode six months later. No investigation of lithiasis was carried out. Regarding family history his maternal grandmother suffered recurrent renal stones. From that point, the episodes became far more frequent, occasionally accompanied by low urinary tract infections of multisensitive-*E. coli*. At the time of the assessment, he was not on any medical treatment. The patient had an athletic phenotype, normotensive, who has a work with moderate physical after which he occasionally has haematuria with voiding symptoms. He denied skin abnormalities or abdominal or joint pain. He did not have repeated infections. Renal ultrasound detected two stones measuring 11 and 15 mm in the left kidney and another two of 6 and 8 mm in the right kidney, which were not causing hydronephrosis; they were radiolucent on the plain abdominal X-ray. Laboratory tests showed normal glomerular filtration rate with moderate haematuria and proteinuria of 0.06 g/day. The lithiasis study showed no significant abnormalities (serum levels of PTH, uric acid, calcium, phosphate, agnesium, calciuria, phosphaturia, uricosuria, magnesiuria, citrate and oxalic acid in urine were normal; urine pH: 5.5). It was estimated a protein intake of 90 g/day and 12 g/day of salt. The immunology study was normal, including IgA. Examination of renal stones revealed an irregular appearance, soft consistency and brown colour, with a composition of 2,8-dihydroxyadenine. He was started on treatment with oral allopurinol and genetic study confirmed the presence in homozygosis of a change of G for T in nucleotide 359, exon 4, which causes a change of glycine for valine in amino acid 120; NM 000485.2 (of the APRT gene): c.359G>T (p.Gly120Val), defined by the Mutation Taster system as of uncertain significance and by Polymorphism Phenotyping v2 and Sorting Intolerant from Tolerant as probably pathological. Not long after starting treatment, the patient suffered further episodes of expulsive renal stones that had to be treated by urethral endocatheterisation. At the time of writing this letter we have no new analyses available to corroborate the efficacy of the proposed treatment.

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Lithiasis formed by 2,8-dihydroxyadenine is caused by an autosomal recessive purine catabolism disorder (OMIM 102600), due to the deficit of the APRT enzyme, this gene consist in five exons and four introns that encode 180 amino acids and is located on chromosome 16q24.3, causes an alteration in the transfer of adenine to AMP and accumulation of 2,8-dihydroxyadenine in the kidneys.[2–4] This disorder was first described in 1968[5] and has a homozygote incidence of 1/50–100,000 people, from 0.4% to 1.2% of heterozygotes,[6] being more common in French, Icelandic and in Japanese people. The underlying genetic disorder determines the differentiation into two types: type 1 is more common in northern Europe, with an absolute deficiency in APRT activity; and type 2 is more common in Japanese people, with APRT activity of 15–20%. More than 40 mutations have been described, although not all of them induce deficiency of enzyme activity.[1,6,7] It may present as progressive chronic renal failure, chronic interstitial damage due to crystal nephropathy or recurrent lithiasis, although they are not always present,[6] or as acute kidney injury.[8–12] Although the enzyme deficit is present in all cells, no extrarenal symptoms have been described. It can recur after renal transplantation[13–16] and alkalinisation of urine is not an effective treatment. Allopurinol may be effective,[8] due to its inhibitory action on the enzyme xanthine dehydrogenase, also febuxostat can be used.[15,17] Both can delay progression and slow down its course. Diagnosis requires the analysis of crystals, characteristically spherical or granular in the form of a fan, birefringent to polarised light and brown in colour,[3] or of the calculus, the composition of which is pathognomonic. The determination of APRT activity in red blood cells and the genetic study are not essential, but they can contribute to the genetic counselling and the certainty of the diagnosis. In some retrospective series,[6] the average delay in diagnosis was of seven years, and even 40 years, which obviously affects the prognosis.

The importance of this case is to characterise a rare cause of chronic renal failure, difficult to identify if it is not linked to recurrent lithiasis, but which is potentially treatable. However, it requires an early diagnosis and the description of a rare mutation, pGly120Val, of uncertain significance, but which, in this case, defines an aggressive nephropathy due to recurrent lithiasis. We believe that APRT deficiency should be suspected in lithiasis with childhood onset, recurring episodes or which lead to chronic renal failure of unclear origin, and the activity of APRT should be systematically quantified in kidney transplant patients who have previously suffered from kidney stones.[8]

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