CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Hypercalciuric nephrolithiasis and nephrocalcinosis caused by CYP24A1 mutations – fourteen years of the patient’s follow-up

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INTRODUCTION

Metabolic disorders are a common cause of nephrolithiasis in childhood [1]. Of these, the most common is hypercalciuria, which is found in 30–50% of children with stones in the urinary system [2]. Hypercalciuria may be associated with normal, increased, or decreased calcium in the blood (Table 1). Hypercalcemic hypercalciuria may be found in hyperparathyroidism, but also in long-lasting immobilization, sarcoidosis, malignancy, juvenile idiopathic arthritis, corticosteroid excess, adrenal failure, William's syndrome, and vitamin D hypervitaminosis.

Historically, vitamin D hypervitaminosis has been mainly attributed to vitamin D intoxication and/or to an intrinsic hypersensitivity to vitamin D [3, 4, 5]. However, with advances in the molecular examination of vitamin D metabolism, our understanding of vitamin D hypervitaminosis significantly improved [6, 7]. Hypersensitivity to vitamin D, which has been observed in earlier studies [4, 5], now may be explained by a gene mutation leading to defective metabolism of active vitamin D [6]. Indeed, mutations of vitamin D 24-hydroxylase (CYP24A1), which normally breaks down both 1,25(OH)₂D₃ and 25(OH)D₃, result in excessive formation of 1,25(OH)₂D₃ [7]. Increased 1,25(OH)₂D₃ levels cause hypercalcemia due to enhanced intestinal calcium absorption and hypercalciuria, because of reduced parathyroid hormone- (PTH) dependent calcium reabsorption in the distal renal tubule [7]. Affected individuals have hypercalcemia and hypercalciuria due to which they are prone to nephrolithiasis/nephrocalcinosis, and consequently renal failure may occur. Being autosomal recessive inherited, this genetic disorder often shows familial occurrence with an increased risk in siblings, who may experience the first clinical signs and diagnosis only in adulthood [8].

It is not rare that nephrolithiasis and nephrocalcinosis caused by CYP24A1 mutations remain unrecognized despite extensive classical evaluation. The aim of our work is to draw attention to hypercalciuria and nephrolithiasis caused by the CYP24A1 gene defects.

CASE REPORT

We report a male Montenegro patient who had primarily presented with microhematuria due to idiopathic hypercalciuria at five years of age.
Renal ultrasound was normal, and he was treated by hydrochlorothiazide. After 12 years, the patient presented with macrohematuria and left-sided renal colic due to nephrolithiasis (Figure 1). He was found to have intermittent borderline hypercalcemia (serum Ca 2.46–2.66 mmol/l), low level of intact PTH (< 0.26 pmol/l), hypercalciuria (11.6 mmol / 24 hours), and increased plasma 25-hydroxy vitamin D \[25(OH)D3\] (137.3 nmol/l). Serum 1,25(OH)2D3 was not measured. The patient denied using vitamin D supplementation, but certainly had a great deal of seasonal sunlight exposure due to Mediterranean climate. Serum electrolytes including magnesium and phosphorus were normal, as well as serum bicarbonate, urea, and creatinine. Twenty-four-hour urine evaluations excluded hyperuricosuria and oxaluria. Also, other causes of hypercalcemia were ruled out. Chemical analysis of stone found calcium oxalate.

During further follow-up of two years the patient was treated with four courses of extracorporeal shockwave lithotripsy, increased water intake, and he was advised to avoid sunlight exposure. At the end of the follow-up he was asymptomatic, and his renal ultrasound was normal, as well as his renal function. The latest biochemical findings were as follows: serum calcium normal (2.34 mmol/l; Ca++ 1.12 mmol/l), intact PTH low (1.37 pmol/l), 25(OH)D3 in the upper normal range (123.5 nmol/l) and increased 24-hour calciuria (8.88 mmol / 24 hours).

The patient’s family history was positive for kidney stones: in the father (at the age of 17 years), the mother (at the age of 35 years) and the paternal grandmother. At the time of this study, renal ultrasound was normal in the parents, but hypercalcemia (2.62 mmol/l), hypercalciuria (12.41 mmol / 24 hours), depressed PTH (1.07 pmol/l) and increased 25(OH)D3 (94.3 nmol/l) were found in the father as well as in our patient. Familial occurrence of nephrolithiasis pointed out its inherited occurrence. Using polymerase chain reaction and Sanger sequencing, a homozygous mutation in \[CYP24A1\] (E143del) was found in the patient and his father, while the mother is heterozygous. The parents declared not to be consanguineous.

### Table 1. The causes of hypercalciuria

<table>
<thead>
<tr>
<th>HEREDITARY HYPERCALCIURIA</th>
<th>ACQUIRED HYPERCALCIURIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normocalcemic hypercalciuria</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Idiopathic Dent’s disease</td>
<td>Drugs: diuretics (furosemide, and acetazolamide), anticonvulsant use (topiramate, zonisamide), ketogenic diet</td>
</tr>
<tr>
<td>Antenatal Bartter syndrome</td>
<td>Familial hypomagnesemia and nephrocalcinosis with hypercalciuria</td>
</tr>
<tr>
<td>Familial renal tubular acidosis</td>
<td>Distal renal tubular acidosis</td>
</tr>
<tr>
<td>Hereditary hypophosphatemic rickets with hypercalciuria</td>
<td>Hypocalcemic hypercalciuria</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Autosomal dominant hypocalcemic hypercalciuria</td>
</tr>
<tr>
<td>Hypercalcemic hypercalciuria</td>
<td>Primary hyperparathyroidism (PHPT)</td>
</tr>
<tr>
<td>MEN1 syndrome-associated PHPT</td>
<td>PHPT sporadic: single parathyroid adenoma, not inherited</td>
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<tr>
<td>Familial isolated PHPT</td>
<td>Long-lasting immobilization</td>
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<tr>
<td>Hyperparathyroidism 2</td>
<td>Sarcoïdosis</td>
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<tr>
<td>Metaphyseal chondrodysplasia Jansen type</td>
<td>Malignancies</td>
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<tr>
<td>Inherited hypophosphatasia</td>
<td>Juvenile idiopathic arthritis</td>
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<tr>
<td>Adrenal failure</td>
<td>Corticosteroid excess</td>
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<tr>
<td>Vitamin D / vitamin A intoxication</td>
<td>Williams Beuren syndrome</td>
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<tr>
<td>Chronic kidney disease</td>
<td>Inherited hypophosphatasia</td>
</tr>
<tr>
<td>Calcium carbonate, lithium</td>
<td>Vitamin D induced infantile hypercalcemia-CYP24A1 gene mutation</td>
</tr>
</tbody>
</table>

DISCUSSION

Our patient as well as his father have an E143del homozygous mutation in \[CYP24A1\]. This mutation, previously described by Schlingmann et al. [9], leads to a complete loss of 25-OH-D3-24-hydroxylase activity that results in persistently increased levels of both 1,25(OH)2D3 and 25(OH)D3 and the absence of any measurable inactive metabolite. Basal renal and extrarenal \[CYP24A1\] is usually low but is highly induced by its substrate 1,25(OH)2D3.

In regulating the level of vitamin D3, \[CYP24A1\] plays a role in calcium homeostasis and the vitamin D endocrine system. Its highest expression is in the intestine, the kidneys, and the skin, where this enzyme acts to remove metabolites of vitamin D [10]. It has been demonstrated that \[CYP24A1\] knockout (−/−) mice suffer from increased sensitivity to exogenous vitamin D intake and approximately half of them die due to severe hypercalcemia [11]. In humans, \[CYP24A1\] mutations can cause idiopathic infantile hypercalcemia (IIH) [12–19], idiopathic hypercalciuria [9], nephrocalcinosis, and possibly reduced bone density [20]. In patients with IIH due to \[CYP24A1\] mutations, even small doses of vitamin D, as prescribed for vitamin D prophylaxis, may provoke symptomatic hypercalcemic
Kidney damage may occur in patients with CYP24A1 mutations, because of nephrolithiasis and/or nephrocalcinosis. It has been estimated that the overall frequency of kidney stones due to CYP24A1 deficiency is 4–20% [20, 21]. However, it probably may be even higher in children as the majority of children with nephrolithiasis have a metabolic background and familial occurrence [1]. Our patient had familial history of nephrolithiasis. His father, who had familial history of nephrolithiasis and urolithiasis in children. Kidney Int. 2011; 80(2):1278–91.


REFERENCES


Увод
Недавно је као узрок хиперкалциуричне нефролитија-зе и нефрокалцинозе откривена инактивациона мутација CYP24A1, гена који кодира витамин Д 24-хидроксилазу. Циљ овог рада је опишемо дуготрајно праћење болесника са хиперкалциуричном мутацијом CYP24A1 у мутацијом.

Приказ болесника
Дечак из Црне Горе први пут је испитан због микрохематурије у петој години живота. Доказана је хиперкалциурија, због које је једно време лечен хидрохлортиазидом. После 12 година поново је јавио хиперкалциурију и левострану нефролитијазу. Доказано су интермитентна хиперкалциемија, низак ниво паратхормона, хиперкалциурија и повећан ниво 25-хидрокси витамина D [25(OH)2D3] у плазми. Болесник није узимао суплементе са витамином Д и сви познати узроци хиперкалциемије су исklучени. Фамилијарна историја је позитивна за нефролитијазу (оба родитеља и баба по оцу), а сличне биохемијске аномалије код оца и сина су указале на наследни поремећај. Откривена је хомозиготна мутација CYP24A1 (E143del) код болесника и његовог оца, док је мајка била хетерозигот. У току даљег праћења од две године болесник је успешно лечен екстракорпоралном литотриписом у четири наврата, али са хиперкалциуријом и ниским нивоем паратхормона у плазми.

Закључак
Код болесника који имају идиопатску хиперкалциурију, нефролитијазу и нефрокалцинозу непознатог порекла, треба испитати витамин Д. Код мутације CYP24A1, витамин D треба избегавати у витаминским суплементима и храни.

Кључне речи: хередитарна нефролитијаза; нефрокалциноза; хиперкалциурија; хипервитаминоза Д; идиопатска хиперкалциемија; хиперкалциурија; идиопатска хиперкалциемија.