SUMMARY

Introduction Recently, inactivation mutations of CYP24A1, the gene encoding vitamin D 24-hydroxylase, were identified in hypercalciuric nephrolithiasis and nephrocalcinosis. Here, we describe a long-term follow-up of a patient with hypercalciuric nephrolithiasis caused by CYP24A1 mutations.

Case outline A male Montenegro patient first presented with microhematuria at the age of five years. Hypercalciuria had been documented and for some time he had been treated by hydrochlorothiazide. After 12 years, the patient presented with macrohematuria and left-sided nephrolithiasis. He was found to have intermittent borderline hypercalcemia, suppressed parathyroid hormone, hypercalciuria, and increased plasma 25-hydroxy vitamin D (25(OH)D). The patient denied any vitamin D supplementation and all other causes of hypercalcemia were ruled out. Positive family history for nephrolithiasis (both parents and grandmother) and similar biochemical abnormalities detected in father and son pointed to an inherited disorder. A homozygous mutation in CYP24A1 (E143del) was found in the patient and his father, while mother is heterozygous. During the follow-up of two years, the patient underwent four extracorporeal shockwave lithotripsies, he was advised to increase water intake, and to avoid sunlight exposure. At the end of follow-up he was asymptomatic, and his renal ultrasound was normal, as well as his renal function, but hypercalciuria and low parathyroid hormone levels persisted.

Conclusion Hypervitaminosis D should be considered in children with idiopathic hypercalciuria, nephrolithiasis and nephrocalcinosis of unknown etiology. Recognition of CYP24A1 mutations in these patients may help to decrease the serious consequences by avoiding vitamin D supplements and excessive sun exposure.

Keywords: hereditary nephrolithiasis; nephrocalcinosis; hypervitaminosis D; idiopathic hypercalcemia

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)D, 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.

**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 D, 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...
crisis which need treatment by acute hemodiafiltration [16]. Increased sensitivity to vitamin D in patients with CYP24A1 mutations has been also documented by seasonal variations of vitamin D and calcium parameters due to sunlight exposure [17, 18]. Calcemia may also be influenced by alimentary factors. Those may explain the intermittent character of hypercalcemia in our patient as well, as he did not receive any vitamin D supplementation. During his first clinical examination at five years of age, it was winter time and investigation did not reveal hypercalcemia, but only hypercalcuria. Therefore, in patients with idiopathic hypercalcuria, serum calcium level should be monitor carefully throughout life.

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 has the identical CYP24A1 mutation and almost identical biochemical alterations, had a kidney stone at adolescent age, but with milder clinical course. It is only uncertain if transient nephrolithiasis in the patient’s mother was the consequence of the heterozygous CYP24A1 mutation. Data from literature suggest that most heterozygous CYP24A1 mutation carriers have a normal vitamin D level, usually are asymptomatic, but may possibly be at an increased risk of nephrolithiasis [22].

Treatment options for CYP24A1 mutation disorders include avoidance of vitamin D supplementation, sunlight exposure and tanning beds, and high water intake, while in severely affected patients, treatment with cytochrome ketoconazole inhibitor may be beneficial [23].

ACKNOWLEDGMENT

Writing of this paper was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, grant No. 175079.

REFERENCES

Сажетак
Увод
Недавно је као узрок хиперкалциуричне нефролитијазе 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 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 се javio због микрохематурије и левостране нефролитијазе. Доказани су интермитентна хиперкалциемија, низак ниво паратхормона, хиперкалциурија и повећан ниво 25-хидрокси витамина Д [25(OH)2D3] у плазми. Болесник није узимао суплементе са витамином Д и сви познати узроки хиперкалцемије су исklучени. Фамилијарна историја је позитивна за нефролитијазу (оба родитеља и баба по оцу), а сличне биохемијске аномалности 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 лечео екстракорпоралном литотрипсијом у четири навраћа, повећаним уносом течности и избегавањем сунчавања. На крају праћења он је био без симптома, нормалне глобалне функције бубрега, нормалног ултрасонографског налаза уринарног тракта, али са хиперкалциуријом и ниским нивоом паратхормона у плазми.
Закључак
Код болесника који имају идиопатску хиперкалциурију, нефролитијазу и хипервитаминозу непознатог узрока, треба испитати витамин Д. Код мутације CYP24A1 избегнути компликације могу се избећи једноставним мерама: избегавање сунчавања и витамина D у витаминским суплементима и храни.
Кључне речи: хередитарна нефролитијаза; нефрокалциноза; хипервитаминоза; идиопатска хиперкалциемија.