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Elżbieta Kuźma-Mroczkowska[1], Agata Poźniak[2], Karol Stachowicz[2],
Hanna Szymanik-Grzelak[1], Małgorzata Pańczyk-Tomaszewska[1]

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Hypercalciuria caused by *CYP24A1* mutation as the cause of recurrent urinary tract infections – a case report

Hiperkalciuria uwarunkowana mutacją genu *CYP24A1* jako przyczyna nawracających zakażeń układu moczowego – opis przypadku

[1] Department of Paediatrics and Nephrology, Warsaw Medical University, Warsaw, Poland
[2] Students' Scientific Association at the Department of Paediatrics and Nephrology, Warsaw Medical University, Warsaw, Poland
Correspondence: Elżbieta Kuźma-Mroczkowska, Department of Paediatrics and Nephrology, Warsaw Medical University, Żwirki i Wigury 63a, 02-091 Warsaw, Poland, tel.: +48 22 317 96 57, e-mail: ekuzma@wum.edu.pl

Abstract

Idiopathic hypercalciuria is the most common metabolic disorder leading to urolithiasis. The following factors are involved in its pathogenesis: environmental and dietary factors, kidney defects leading to excess loss of calcium in urine, conditions characterised by increased bone calcium resorption, and genetic mutations impairing vitamin D metabolism. The severity of hypercalciuria may vary, from vitamin D intoxication, through nephrocalcinosis, urolithiasis, hypercalciuria, to milder forms, which occur during vitamin D supplementation. Hypercalciuria may produce non-specific symptoms, such as erythrocyturia, haematuria, sterile leukocyturia, and urinary tract infections. We present a case of a 10-year-old girl with recurrent urinary tract infections. Following the exclusion of urinary tract defect and urinary bladder dysfunction, the patient was diagnosed with renal hypercalciuria. Genetic testing confirmed *CYP24A1* mutation. Treatment with thiazides resulted in calciuria normalisation and resolution of recurrent urinary tract infections. **Conclusions:** Genetic hypercalciuria should be suspected in patients with recurrent urinary tract infections.

Keywords: *CYP24A1* mutations, hypercalciuria, urinary tract infections

Streszczenie

Hiperkalciuria idiopatyczna jest najczęstszym zaburzeniem metabolicznym prowadzącym do rozwoju kamicy układu moczowego. W jej powstaniu odgrywają rolę: czynniki środowiskowe i dietetyczne, defekty nerkowe – prowadzące do nadmiernej utraty wapnia z moczem, stany przebiegające z nadmierną resorpcją wapnia z kości, mutacje genetyczne zaburzające metabolizm witaminy D. Objawy hiperkalciurii mogą być różnie nasilone – od zatrucia witaminą D, poprzez nefrokalcynozę, kamicę, hiperkalciurię, do postaci łagodniejszych, które ujawnią się podczas suplementacji witaminą D. Hiperkalciuria może powodować niespecyficzne objawy, takie jak: krwinkomocz, krwiomocz, jałowa leukocyturia, zakażenia układu moczowego. W pracy przedstawiono opis przypadku 10-letniej dziewczynki z nawracającymi zakażeniami układu moczowego, u której wykluczono wadę układu moczowego i zaburzenia funkcji pęcherza, stwierdzono zaś hiperkalciurię nerkową. Badania genetyczne potwierdziły mutację *CYP24A1*. Leczenie tiazydami spowodowało normalizację kalciurii, nawroty zakażeń układu moczowego ustąpiły. **Wnioski:** U pacjentów z nawrotami zakażeń układu moczowego należy brać pod uwagę możliwość występowania hiperkalciurii o podłożu genetycznym.

Słowa kluczowe: mutacja *CYP24A1*, hiperkalciuria, zakażenia układu moczowego

INTRODUCTION

Idiopathic hypercalciuria (IH) is defined as excessive urinary calcium excretion of >4 mg/kg/day. Calcium-creatinine index (UCa/Cr) in a morning urine sample is also used in the diagnosis. Reference values used in this method depend on patient's age, and the interpretation of results may pose difficulty due to different standards proposed by different authors[1]. Hypercalciuria is the most common metabolic disorder leading to urolithiasis. Adults and children account for 30–60% and 40%, respectively, of patients in this group[1,2].

Based on the findings to date, and the probable pathomechanism, absorptive, renal and resorptive hypercalciuria may be distinguished. Absorptive hypercalciuria is caused by increased gastrointestinal absorption of calcium, which may result from increased dietary calcium supply, vitamin D over-supplementation or impaired vitamin D metabolism. Renal hypercalciuria is caused by defective calcium reabsorption, whereas increased resorption from bones due to e.g. long-term corticosteroid therapy, immobilisation, tumour metastases to bones or hyperparathyroidism, leads to resorptive hypercalciuria[3,4]. Pak's test (oral calcium tolerance test) is used for differentiation of hypercalciuria depending on the aetiology. Recently, it has been emphasised that the above mentioned types of hypercalciuria may interweave and represent a clinical manifestation of a single condition[1].

The symptoms of hypercalciuria include nephrolithiasis, abdominal pain, dysuric symptoms, erythrocyturia, haematuria, sterile leukocyturia, and recurrent urinary tract infections. Skeletal symptoms associated with reduced mineral bone density, such as arthralgia and pathological fractures, may also occur[5,6].

CASE REPORT

The paper describes a case of a 10-year-old girl in whom extended diagnosis of the causes of recurrent urinary tract infections revealed genetic hypercalciuria.

The girl was 7 years old when she was first admitted to the Department of Paediatric Nephrology. Abdominal ultrasound and miction cystography excluded urinary tract defects. Uroflowmetry (urodynamics) was normal. Dynamic renal scintigraphy showed small post-inflammatory lesions in the left kidney. Due to the presence of a kidney stone on ultrasound (4 mm in diameter, left kidney parenchyma), the diagnosis was extended to include calcium-phosphorus metabolism (Tab. 1). Serum findings were as follows: reduced 25(OH)D, $1,25(OH)_2D$ in the upper limit of normal, calcaemia in the upper limit of normal; 24-hour urine collection: increased excretion of calcium, phosphorus and sodium, increased calcium/creatinine and phosphorus/creatinine ratio. Urinary citrate excretion was 0.97 mmol/1.73 m^2/day. The diagnosis was extended to include Pak's test. The Uca/Cr ratio [mg/mg] was 0.4 before

Parameter	Age [years]								
	7	7.5	7.75	8	8.5	9.0	9.5	10	10.5
Creatinine [mg/dL], reference range: 0.2–0.7	0.4		0.4		0.4				0.4
Calcium [mEq/L], reference range: 4.38–5.3	5.3		5.3		5.2				5.1
Phosphorus [mEq/L], reference range: 2.16–3.24	2.7		2.9		3.0				2.9
Magnesium [mg/dL], reference range: 1.6–2.3	2.1		2.1		2.1				2.0
Sodium [mmol/L], reference range: 132–145	145		142		143				140
25(OH)D [ng/mL], reference range: 20–50	7.5		19.9		27				28
$1,25(OH)_2D$ [pg/mL], reference range: 19.9–79.3			61.4						
PTH [pg/mL], reference range: 11–67	10.4		11.8						
Alkaline phosphatase [U/L], reference range: 156–386	164		203						230
Mineral excretion [mg/kg/day]									
Calcium	6.02	8.22	6.15	7.52	5.03	3.13	2.45	5.2	3.7
Phosphorus	28.26	14.7	23.9	20.7	12.6	15	14.7	13	13.5
Magnesium	2.72	2.76	4.37	2.07	1.94	2.8	2.42	2.27	2.7
Uric acid	13.41	12.8	15.6	10.5	10.4	14	13	9	8
Creatinine	16.71	17.8	18.6	18.1	18.6	18.5	21	18.4	18.6
Sodium excretion [mmol/kg/day]	4.16	3.13	2.0	2.61					
Calcium/creatinine ratio	0.36	0.46	0.33	0.41	0.27	0.17	0.12	0.28	0.19
Phosphorus/creatinine ratio	1.71	0.82	1.29	1.14	0.68	0.8	0.7		0.72
Magnesium/creatinine ratio	0.16	0.15	0.23	0.13	0.1	0.15	0.11	0.12	0.14
Magnesium/calcium ratio	0.46	0.33	0.71	0.33	0.39	0.89	0.98	0.43	0.7
Fe Mg [%]	3.13		3.13						
Vitamin D_3 supplementation [U/day]	0	400	0	200	200	200	200	400	600
Hydrochlorothiazide [mg/day]						12.5	12.5	12.5	25

Tab. 1. Biochemical parameters evaluated during observation and treatment

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Ca load and 0.73 after Ca load. The results suggested renal hypercalciuria. Densitometry showed reduced total bone mineral density [BMD of 0.746 g/cm^2, Z-score (–1.4)], especially in the lumbar spine [L2–L4 BMD – 0.5 g/cm^2, Z-score (–2.4)]. A decision was made to run genetic tests, which detected a heterozygous mutation in *CYP24A1* (p.R396W) coding for 1,25(OH)$_2$D-24-hydroxylase. The treatment was initially based on diet with a limited phosphate and salt intake, and a normal calcium intake, which normalised phosphaturia, with no effects on hypercalciuria. Vitamin D$_3$ supplementation was initiated due to its low levels and reduced BMD. However, an increase in both stone diameter and hypercalciuria was observed. Hydrochlorothiazide was included. The dose was individually adjusted; calciuria and 25(OH)D were monitored. Vitamin D supplementation was discontinued during the summer months. Currently, calcium–phosphate metabolism parameters are within normal limits. Ultrasonography shows no increase in the size if the stone. The girl has developed no urinary tract infections for a year. Follow-up densitometry showed no reduction in total BMD [total BMD – 0.781 g/cm^2, Z-score (–1.3)], and a progression in the lumbar spine [L2–L4 BMD – 0.502 g/cm^2, Z-score (–2.8)]. The patient remains under the care of an orthopaedist and a physiotherapist.

DISCUSSION

Idiopathic hypercalciuria in children is a metabolic disorder leading to nephrolithiasis[1,5–7]. The disorder is characterised by normocalcaemia and hypercalciuria, which occurs without any obvious reason. The etiopathology includes environmental (global warming), dietary (diet low in calcium and magnesium) and genetic factors[1,8]. *CYP24A1*, which was found to be defective in our patient, codes for 1,25(OH)$_2$D-24-hydroxylase. This enzyme acts on both calcidiol [25(OH)D] and calcitriol [1,25(OH)$_2$D], leading to the formation of their inactive catabolites: 24,25(OH)$_2$D and 1,24,25(OH)$_3$D[9]. The 24-hydroxylation is an important mechanism preventing vitamin D intoxication[5,10]. A defect in *CYP24A1* results in active vitamin D accumulation in the body and the development of clinical symptoms of its excess, such as increased bone resorption, increased intestinal absorption and renal excretion. This condition is known as idiopathic infantile hypercalcaemia[5,6,10,11], and may occur with or without hypercalcaemia[3]. It is generally believed that although a homozygous mutation results in a more severe disease, with severe hypercalcaemia in the first year after birth, even these patients may show scarce symptoms in the course of the disease[5,11]. A comparison of the presented case characterised by diagnostically difficult, insidious course with cases of *CYP24A1* mutation described in the literature indicates that the clinical course of this disorder may show considerable interpatient variability. Acute cases with severe hypercalcaemia already in the first year of life[6] as well as cases diagnosed not earlier than in early childhood or even adulthood have been described[7]. Polymorphisms of *CYP24A1* may be associated with both mild and more severe manifestations in the form of nephrolithiasis or nephrocalcinosis[9]. It should be noted at this point that there are other genetic disorders that can produce a similar clinical picture. In addition to *CYP24A1* mutation, other causes of idiopathic infantile hypercalcaemia may include Williams–Beuren syndrome caused by deletion on chromosome 7 and mutations of *SLC34A1*, a gene coding for sodium phosphate cotransporter[5,8].

In the case of our patient, recurrent urinary tract infections were initially the only symptom. Identification of a kidney stone suggested that the disease process had begun long before the diagnosis. Reduced BMD conformed its chronic nature. Osteopenia/osteoporosis is common in patients with idiopathic hypercalciuria[12]. The aetiopathogenesis of bone disorders is multifactorial, but not fully understood. They may be caused by, among other things, unhealthy diet (high-protein diet with limited calcium intake), abnormal calcitriol levels or genetic predispositions. It was also reported that children with hypercalciuria and stones show lower skeletal calcification compared to children with hypercalciuria, but with no nephrolithiasis[12].

The treatment of idiopathic hypercalciuria involves the use of thiazide diuretics, which directly increase calcium reabsorption at the distal tubule, and thus reduce calciuria[3,6]. Although thiazides prevent stone formation in the urinary tract, their contribution to improved bone mineral density is disputable. Therapeutic difficulties in choosing the dose of vitamin D still remain an important problem in this group of patients. Currently, the use of vitamin D preparations is very common due to its widespread deficiency. Studies to date have shown no relationship between vitamin D intake and an increased risk of kidney stones. There are no guidelines on vitamin D dosage in children with hypercalciuria and kidney stone disease. Although proper vitamin D supplementation is very important for normal growth in this group of patients, it may increase calcium excretion. However, the diagnosis of 1,25(OH)$_2$D-24-hydroxylase deficiency has significant implications, especially in patients with high urine calcium, high serum calcium, and low parathyroid hormone (PTH)[9]. It is emphasised that prophylactic doses of vitamin D administered in individuals without diagnosed mutation may trigger symptoms of intoxication with this compound. Therefore, despite the unquestionable benefits resulting from vitamin D supplementation, its use requires some caution[10]. It seems that a decision to discontinue or continue vitamin D supplementation and the selection of an appropriate dose should be determined individually in patients with a known *CYP24A1* defect, with constant monitoring of calciuria, calcaemia, alkaline phosphatase activity as well as 25(OH)D and 1,25(OH)$_2$D levels[11,12].

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CONCLUSIONS

Calcium disorders should be considered and calciuria should be assessed in children with recurrent urinary tract infections.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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