Idiopathic infantile hypercalcemia: Mutations in *SLC34A1* and *CYP24A1* in two siblings and fathers

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Introduction

Both *CYP24A1* and *SLC34A1* gene mutations are responsible for idiopathic infantile hypercalcemia (IIH). Whereas loss-of-function mutations in *CYP24A1* (25-OH-vitamin D-24-hydroxylase) lead to a defect in the inactivation of active 1,25$(OH)_2$-vitamin D_3, mutations in *SLC34A1* encoding renal sodium-phosphate co-transporter NaPi-IIa lead to primary renal phosphate wasting combined with an inappropriate activation of vitamin D. The presence of mutations in both genes has not been reported in the same patient until today.

Case Reports

Case 1: A 13-month-old boy was hospitalized with a diagnosis of UTI. The urinary system ultrasonography revealed nephrocalcinosis and laboratory analyses detected a serum calcium value of 16.7 mg / dL. The family history revealed kidney stones in the father's uncle and aunt. He received 400 IU of vitamin D and 480 mg calcium per day.

Upon diagnosis of hypercalcemia, oral vitamin D and calcium intake was stopped. Intensive intravenous rehydration and furosemide were initiated. Because serum phosphorus levels were found to be low, oral phosphorus was started. On the tenth day of therapy, serum calcium was 10.59 mg/dL(Figure 1). All treatments were discontinued and the patient was discharged from hospital. On admission, the patient had normal renal size but bilateral medullary nephrocalcinosis was detected. At the last visit he was 8.48 years old. Weight and height were normal. Hypercalcemia and nephrocalcinosis were not detected (Table 1).

Case 2: Sister of case 1. 21 months after the initial presentation of her older brother, a 6-months-old girl was admitted to hospital because of vomiting. Biochemical investigation of the patient revealed hypercalcemia. Intensive intravenous rehydration was started. The control of her serum Ca level was found to be high and the girl was referred to the pediatric endocrine clinic.

Furosemide and methylprednisolone were given together with intensive intravenous rehydration. Despite treatment, her serum Ca levels remained within the upper normal range (Figure 2). USG revealed a double collecting system on the left side and bilateral medullary nephrocalcinosis. At admission, the physical examination was normal. Anthropometric measurements and laboratory results are provided in Table 2. On the 19th day of hospitalization, the patient was discharged from the hospital without any medication.

On follow-up, serum calcium and phosphorus levels were within normal range (Table 2). Intermittent ultrasonographic examinations revealed no improvement of nephrocalcinosis. On the latest visit, the patient was 6 years old. There were no signs of developmental delay or mental-motor retardation. However bilateral medullary nephrocalcinosis persisted at the latest ultrasonographic examination.

Parents: At the last visit of both children, laboratory evaluations of the parents were performed. Both of them had no clinical complaint. The results of laboratory investigation are provided in Table I. Both parents exhibited a low tubular phosphate reabsorption (TRP) , however only father had nephrocalcinosis.

Siblings and their parents all carry a homozygous stop codon mutation (p.R466*) in *CYP24A1*. Interestingly both siblings and the father also have a heterozygous splice-site mutation (IVS6(+1)G>A) in *SLC34A1*.

Table 1: Clinical and Laboratory Findings of the Case 1 at The Admission and Follow-up

Case 1	At the admission	At the 4.16 years old	At the 5.4 years old	8.48 years-old
Weight, kg (SD)	10.5 (-0.01)	21 (1.46)	22.8 (1.11)	32.5 (1.2)
Height, cm (SD)	77 (-0.42)	109.5 (1.03)	119.8 (1.54)	134.5 (0.92)
Ca, mg/dL, (8.8-10.8)	16.7	10.7	10.8	9.9
P, mg/dL (3.8-6.5)	2.3	5.8	5.9	4.9
ALP, IU (<420)	179	250	216	256
PTH,pg/mL (12-88)	<6	15.3	23.8	39.9
Mg, mg/dL (1.7-2.3)	1.96		2.3	2.3
25 OH D3, ng/mL (10-70)	6.9	16.5	14.2	12.4
1,25 OHD3, pg/mL (19.6-65)	19.9	11	15.1	20.21
Na, mEq/L	133			

Table 3: Laboratory Findings of the Parents

At the last visit	Father	Mother
Age, year	39	31
Ca, mg/dL (8.4-10.7)	9.8	9.5
P, mg/dL (2.3-4.7)	4.7	2.9
ALP, IU (44-147)	116	83
PTH,pg/mL (12-88)	12	22.7
Mg, mg/dL (1.7-2.3)	2.16	1.94
25 OH D_3, ng/mL (10-70)	11.2	16.4
1,25 $(OH)_2D_3$, pg/mL (19.6-65)	12.74	26.06
Na, mEq/L	140	137
Spot Urine Ca/creatinin,	0.22	0.05

Table 2: Clinical and Laboratory Findings of the Case 2 at The Admission and Follow-up

Case 2	At the admission	At the 1.08 years old	At the 1.80 years old	At the 2.4 years old	6 years old
Weight, kg (SD)	7.4(0.03)	9.15 (-0.32)	10.9(-0.14)	14(-0.04)	18 (-0.95)
Height, cm (SD)	67 (0.27)	73.5(-0.74)	82.5(-0.36)	93.5(-0.34)	113.5(-0.39)
Ca, mg/dL, (8.8-10.8)	17.3	10.7	9.9	10.3	10.6
P, mg/dL (3.8-6.5)	3.8	5.7	4.5	5.9	5.2
ALP, IU (<420)	71		175	177	170
PTH, pg/mL (12-88)	<6		9.1	26.5	10.8
Mg, mg/dL (1.7-2.3)	1.99			2.07	2.04
25 OH D3, ng/mL (10-70)	18.91		19.4	11.7	22.4
1,25 OHD3, pg/mL (19.6-65)	47.56		19	13.6	23.17
Na, mEq/L	139				
Spot Urine Ca/creatinin,	1.7	0.82	1.0	0.59	0.54
TRP, % (85-90)	82				87
Creatinin, mg/dL	0.29				0.56

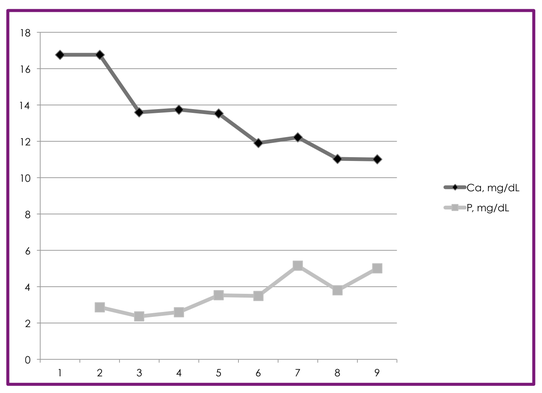

Figure 1: Serum Calcium and Phosphor Levels of the Case 1 at the Admission

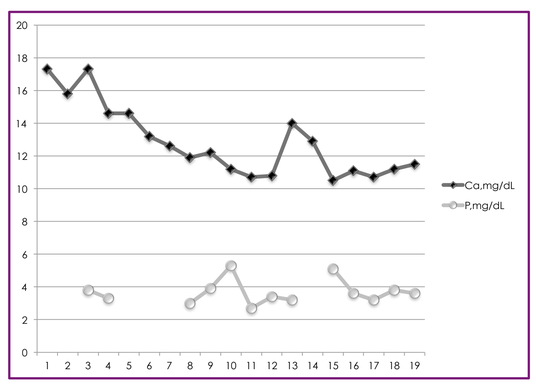

Figure 2: Serum Calcium and Phosphor Levels of the Case 2 at the Admission

Conclusion:

We conclude that a bi-allelic loss-of-function mutation in the *CYP24A1* gene was identified as responsible for hypercalcemia, hypercalciuria and nephrocalcinosis in the family. In addition, a heterozygous mutation in the *SLC34A1* gene although not being the main pathogenic factor, might contribute to the severe phenotype of both patients and their father.