Nephrocalcinosis in an Adult Patient with Idiopathic Infantile Hypercalcemia and a Novel CYP24A1 Mutation

LANDESKRANKENHAUS FELDKIRCH
Universitäres Lehrkrankenhaus

K. Lhotta, A. Mündlein, E. Meusburger and E. Zitt
Dept. of Nephrology and Dialysis, Vorarlberg Institute for Vascular Investigation and Treatment, Academic Teaching Hospital Feldkirch, Austria

INTRODUCTION AND AIMS:
Idiopathic infantile hypercalcemia is a rare autosomal recessively inherited disease, presenting in the first year of life by vitamin D supplementation. Recently loss-of-function mutations in the CYP24A1 gene encoding 24-hydroxylase, an enzyme that inactivates vitamin D metabolites, have been found in these patients.

METHODS:
An investigation of calcium and phosphate metabolism including vitamin D metabolites and FGF23 measurement was done in a patient, who had suffered from idiopathic infantile hypercalciuria and presented with nephrocalcinosis, and his family members. Additionally, sequence analysis of The CYP24A1 gene was performed.

RESULTS:
We here describe a young man homozygous for a novel missense mutation (c.628T>C) of the CYP24A1 gene. In silico analysis predicted that the W210R mutation is damaging to the protein. The mutation was not found in 514 controls. The patient had suffered from severe hypercalcemia in early childhood. At age 29 years he presented with medullary nephrocalcinosis, chronic kidney disease stage 2, microalbuminuria, mild hypertension and nephrogenic diabetes insipidus. He had mild hypercalcemia and moderate hypercalciuria und hyperphosphaturia. Serum 24,25(OH) vitamin D3 was reduced, 25(OH) vitamin D3 and calcitriol were normal, parathyroid hormone suppressed and fibroblast growth factor 23 was elevated. Both parents and two siblings, all heterozygous for the mutation, were healthy.

FIGURE 3: family tree.Both parents and both siblings are heterozygous for the W210R mutation

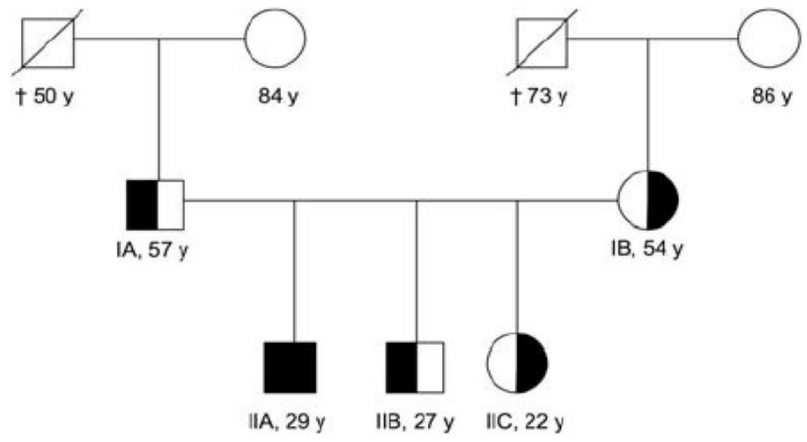
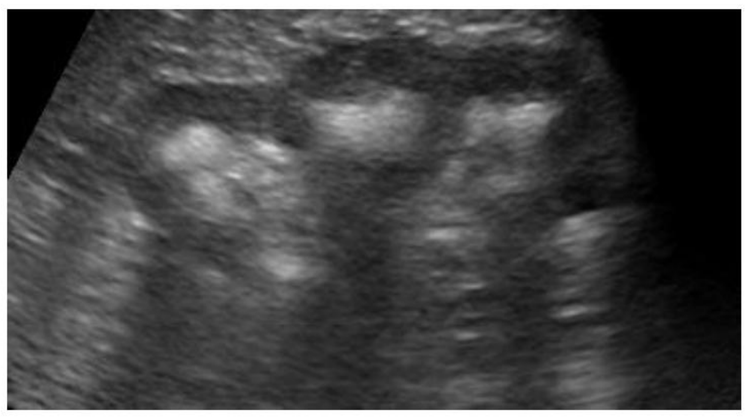


TABLE 1. Laboratory results of all family members

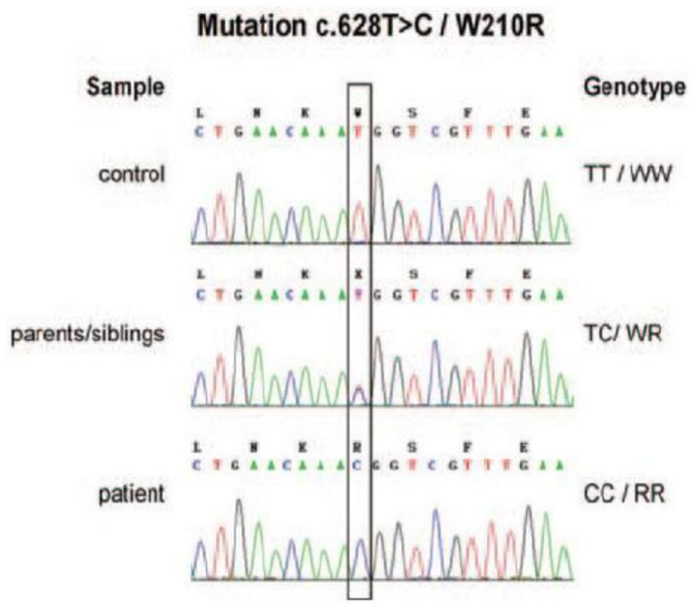
Family member	IA	IB	IIA	IIB	IIC
Age (years), gender	57, m	54, f	29, m	27, m	22, f
W210R	heteroz.	heteroz.	homoz.	hetercz.	zeteroz.
Creatinine (0.7-1.2 mg/dL)	1.0	0.9	1.4	0.9	0.7
Calcium (2.15-2.55 mmol/L)	2.25	2.33	2.61	2.51	2.36
Phosphate (0.81-1.45 mmol/L)	1.05	0.95	0.84	0.80	0.75
PTH (15-65 pg/mL)	39	30	13	24	16
25(OH) Vitamin D_3 (30-100 ng/mL)	24.4	20.8	28	18.7	38
1,25$(OH)_2$ Vitamin D_3 (20-63 ng/L)	39	32	41	74	55
24,25$(OH)_2$ Vitamin D_3 *(1,2-2,6 ng/mL)	2.5	2.0	0.6	2.2	5.4
24,25$(OH)_2$/25(OH)	0.10	0.10	0.02	0.12	0.14
FGF23** (0-125 RU/mL)	79	76	302	64	48
Urinary Ca/Cr (<0.2 g/g)	0.087	0.052	0.219	0.106	0.047
TRP (82-90%)	85%	84%	70%	79%	81%
TmP/GFR (0.8-1.4 mmol/L)	0.9	0.9	0.6	0.7	0.7

FIGURE 1: Ultrasound of the patient‘s right kidney



CONCLUSIONS:
We report a novel CYP24A1 mutation in an adult patient with nephrocalcinosis. An elevation of FGF23 with consecutive hyperphosphaturia, which may contribute to the development of nephrocalcinosis, is reported for the first time in idiopathic infantile hypercalciuria. In addition to low calcium diet and avoidance of nutritional vitamin D we propose sun protection to treat such patients.

FIGURE 2. DNA sequencing chromatographs



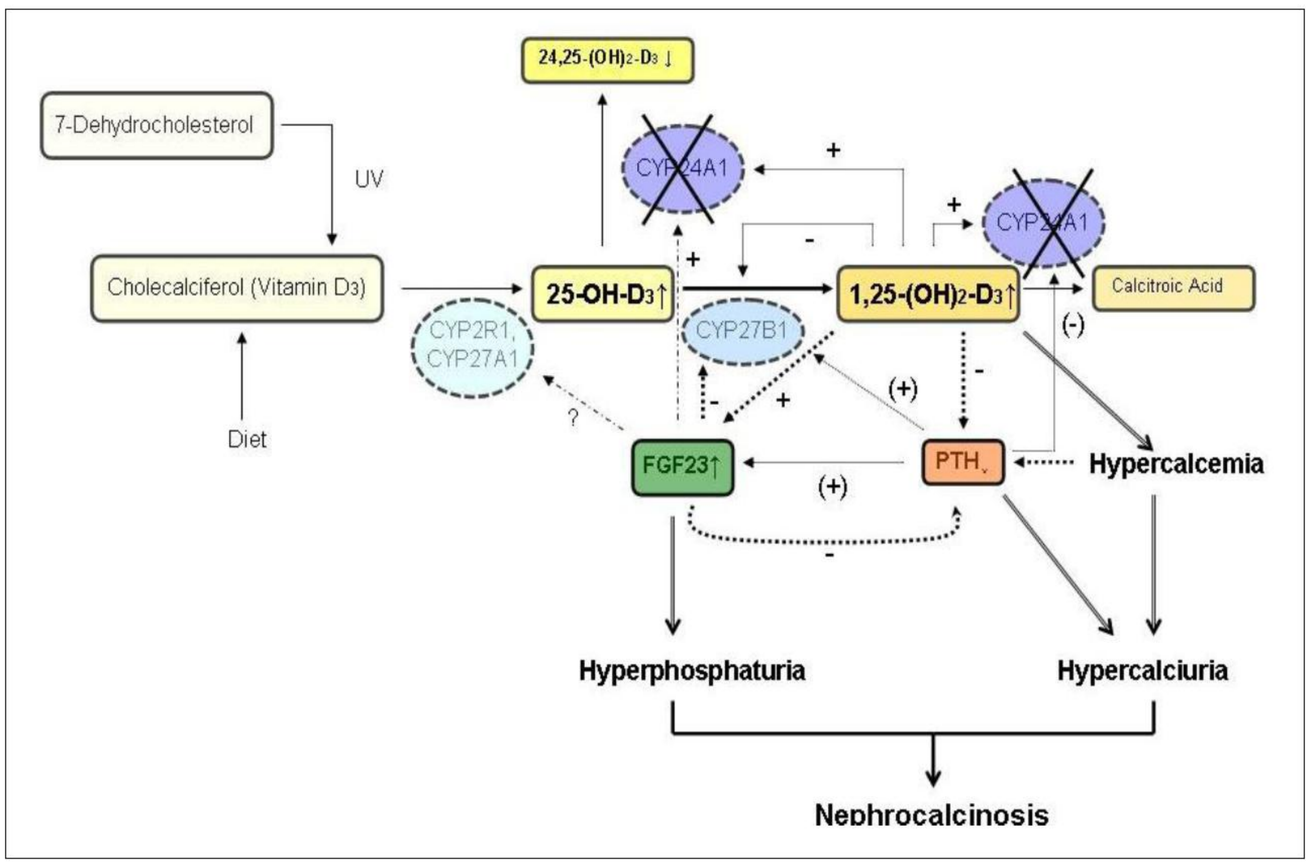


FIGURE 4. A model for the pathogenesis of IIH

Due to the W210R missense mutation CYP24A1 activity is reduced resulting in increased levels of 25(OH)D3 and reduced levels of 24,25(OH)2D3. Increased 1,25(OH)2D3 (normalizing over years due to adaptive mechanism, but inadequately high given the hypercalcemia) suppresses PTH levels and enhances FGF23 secretion. Low PTH and high FGF23 decrease CYP27B1 activity resulting in normal levels of 1,25(OH)2D3 over time. Hypercalcemia and low PTH cause hypercalciuria which leads to nephrocalcinosis, further aggravated by the hyperphosphaturia caused by high FGF23 levels.

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Karl Lhotta
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