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DON'T FORGET THE CALCIUM WHEN EVALUATING HYPOTONIA – CASE REPORT OF IDIOPATHIC INFANTILE HYPERCALCEMIA

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Abstract

Idiopathic infantile hypercalcemia (IIH) is a rare genetic autosomal recessive disease characterized by hypercalcemia, hypercalciuria, and suppressed parathormone levels. It presents with a variety of clinical features, such as vomiting, dehydration, polyuria, lethargy, hypotonia, constipation, and poor weight gain. Renal ultrasonography demonstrates medullary nephrocalcinosis.

This report presents a case of a 7-month-old male infant admitted for further investigation. The motive for hospitalization was lethargy, hypotonia, poor appetite, and poor weight gain. Biochemical findings revealed hypercalcemia, elevated vitamin D3 levels, suppressed intact parathormone levels, polyuria, hypercalciuria, and bilateral medullary nephrocalcinosis on renal ultrasound. The diagnosis was confirmed by sequence analysis of the coding exons of the gene *CYP24A1* on the genomic DNA of the patient and identified two pathogenic variants of the gene.Therapy with a short oral course of prednisolone, and dietary management with reduction of calcium and cessation of vitamin D intake had a satisfactory effect on the progress of body weight, improved motor skills, and normalized laboratory findings.

In this case, we want to emphasize that when examining a child with hypotonia, we should always consider electrolyte disorders, in this case, hypercalcemia.

***Keywords**:* Idiopathic infantile hypercalcemia, *CYP24A1*, nephrocalcinosis, hypotonia.

Introduction

Idiopathic infantile hypercalcemia (IIH) is a rare genetic autosomal recessive disease characterized by hypercalcemia, hypercalciuria, suppressed intact parathormone levels, and nephrocalcinosis. It presents with a variety of clinical features, such as vomiting, dehydration, polyuria, lethargy, hypotonia, constipation, and poor weight gain [1]. Two types of the disease are described, type 1 and type 2 with mutations in two genes, *CYP24A1* and *SLC34A1* [2].

It should be distinguished from William Beuren syndrome, which has almost identical biochemical and clinical characteristics but in William Beuren syndrome patients have also typical dysmorphic facial features, congenital cardiopathy and intellectual disability. Vitamin D therapy even prophylactic doses can be toxic for these patients, emphasizing the importance of early recognition of this disease and exclusion of vitamin D [3].

In this case report we present a 7-month-old male infant who was investigated due to hypotonia and failure to thrive, after further workup the clinical diagnosis of IIH was confirmed with mutational analysis of the *CYP24A1* gene.

Case Report

A 7-month-old male infant of Albanian origin was referred for investigation of hypotonia. The baby was born at term, with a BW of 3560 grams, a BL of 51 cm, and an Apgar score of 7/9. He was the first child in the family, from non-consanguineous parents.

On admission to the hospital, he weighed 6.5 kg (<3 percentile, Z score -2.52) and was 68 cm tall (25th percentile). From the detailed history, we were informed that the baby did not drink enough milk, vomited very often, and did not gain weight. A pronounced hypotonia was observed on physical examination. Magnetic resonance of the brain was normal. The laboratory parameters showed normal hematology parameters and no disturbances in acid-base status. Since mild hydronephrosis was seen in this child after birth, he was referred for a renal ultrasound. A pronounced nephrocalcinosis was revealed. Then, the biochemical parameters that were previously done were analyzed again and it was found that the child had a hypercalcemia.

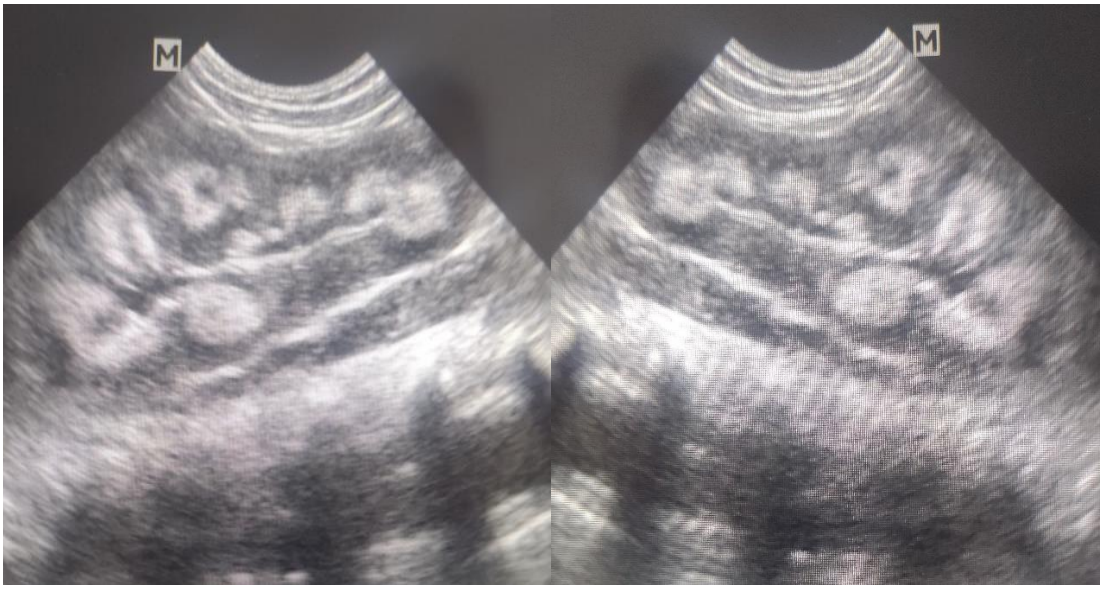

Figure 1 Bilateral medullary nephrocalcinosis on renal ultrasound

Biochemical parameters: glucose 4.29 mmol/l, urea 6.8 mmol/l, creatinine 26.7 μmol/l, cystatin C 1.2 mg/l, uric acid 320.7 μmol/l, sodium 135 mmol/l, potassium 4.0 mmol/l, chlorides 104 mmol/l, calcium 3.12 mmol/l, magnesium 1.07 mmol/l, serum osmolality 262 mosm/kg, total proteins 69 g/l, albumins 37 g/l, AST 24 U/l, ALT 59 U/l, GGT 18 U/l, LDH 483 U/l, alkaline phosphatase 144 U/l, creatinine kinase 27 U/l, iPTH 1.2 pg/ml, 25 (OH) Vit D3 107.8 ng/ml. Urine analysis sodium < 20 mmol/l, potassium 12.3 mmol/l, chlorides <20 mmol/l, calcium 2.08 mmol/l, phosphates 6.04 mmol/l, magnesium 1.26 mmol/l, creatinine 0.553 mmol/l, glucose 0.08 mmol/l, proteins <68 mg/l, urea 35.9 mmol/l, uric acid 0.682 mmol/l, urinary calcium/creatinine ratio= 3.76 mmol/mmol, beta 2 microglobulin 0,06 mg/l.

The clinical picture and laboratory parameters enabled the diagnosis of the patient. The infant was treated with saline solution rehydration and low-dose prednisolone. Vitamin D supplements were stopped immediately, and a special milk formula with reduced amounts of calcium was introduced. The mother was educated to avoid foods with large amounts of calcium. He was discharged with serum calcium of 2.7 mmol/l and at that moment therapy with prednisolone was stopped.

The baby was seen regularly at the outpatient Clinics, and three months later he showed marked improvement in growth, motor skills, and biochemical parameters. The baby's weight was 8 kg (3rd percentile) and length was 74 cm (50th percentile). Serum calcium was 2.53 mmol/l, 25 (OH) Vit D3 26.9 ng/ml, and parathormone 11.9 pg/ml. The urinary calcium/creatinine ratio was within referent values of 0.2 mmol/mmol.

Sanger sequencing analysis of the coding exons of the gene *CYP24A1* on genomic DNA identified (*likely*) *pathogenic CYP24A1* variants c.428_430del and c.1147G>C thus confirming the compound-heterozygosity of both variants. It was identified the pathogenic deletion c.428_430del in exon 2 [p.(Glu143del)] of the *CYP24A1* gene in the heterozygous state, resulting in the deletion of the glutamic

acid residue at position 143 of the protein sequence and additionally another likely pathogenic heterozygous sequence variant c.1147G>C in exon 8 of the *CYP24A1* gene – leading to an amino acid exchange from glutamic acid to glutamine at the amino acid position 383 [p.(Glu383Gln)]. Mother was a heterozygote carrier of the first variant and father of the second variant.

Discussion

The first key element in this child that led us to the diagnosis was nephrocalcinosis together with hypercalcemia. When diagnosing a child with renal medullary hyperechogenicity, all biochemical parameters that may lead to it are considered. One of the reasons could be distal renal tubular acidosis, but in our patient, we had a normal anion gap and urine pH was 5. Also, urate nephropathy was ruled out because the uric acid level in the blood and uricosuria were within normal limits [4]. Another similar condition with identical biochemical parameters is Williams-Beuren syndrome. However, patients with this syndrome have typical facial dysmorphia (elfin face), congenital cardiopathy, and intellectual disability, caused by microdeletion of the 7th chromosome (7q11.23) that involves the elastin gene [5]. When evaluating hypotonia and failure to thrive in an infant it is necessary to initially assess food intake and diuresis. In our case the patient was polyuric but this was not noticed in the first evaluation. Electrolyte and acid-base abnormalities may also indicate a specific metabolic, endocrine, or renal disease [6-8].

Hypercalcemia accompanied by suppressed intact parathyroid hormone levels, hypercalciuria, and nephrocalcinosis were sufficient to suspect idiopathic infantile hypercalcemia in our patient.

Mutations in two genes - *CYP24A1* and *SLC34A1* cause type 1 and type 2 of IIH. The molecular basis for IIH type 1 was first described in 2011 in a cohort of six patients. Mutations in the *CYP24A1* gene which encodes 25-hydroxyvitamin D 24-hydroxylase, the key enzyme of 1,25-dihydroxy vitamin D3 degradation, is the key mechanism of developing hypercalcemia in these patients due to the accumulation of active metabolite 1,25-dihydroxy vitamin D3 [9]. Later, in 2016 the same group of authors found the second gene responsible for type 2 IIH. Autosomal-recessive loss-of-function mutations in the *SLC34A1* gene encode the renal sodium-phosphate cotransporter NaPi-IIa. The mechanism is different, these patients exhibit hypophosphatemia due to renal phosphate wasting. Subsequent hypophosphatemia induces a decrease in circulating FGF23 levels, together hypophosphatemia and low FGF23 levels are known to increase 1α-hydroxylase activity as well as inhibiting 24-hydroxylase activity, with subsequent hypercalcemia [10].

The clinical manifestation of *CYP24A1* mutation can be very variable, manifesting predominantly in the first year of life with severe manifestation, but also can be manifested later in life even in adult age with nephrolithiasis, nephrocalcinosis, and chronic kidney disease. [11,12] *CYP24A1* mutations should be considered in the differential diagnosis of hypercalciuric nephrolithiasis, especially as many adults are now prescribed supplemental oral vitamin D [13]. In these patients, periods of increased sunlight exposure correlate with decreases in PTH levels and increases in levels of serum and urine calcium [14]. Subjects with IIH have a greater risk of progressive chronic kidney disease. In one study in Poland, in 18 genetically confirmed cases of IIH, long-term outcome was analyzed. The average glomerular filtration rate was 72 mL/min/1.73 m2 (range 15-105). Two patients with a *CYP24A1* mutation developed ESRD and underwent renal transplantation. This dictates that all patients should be closely monitored, with early implementation of preventive measures, e.g. inhibition of active metabolites of vitamin D3 synthesis [15]. There are some promising data but, the long-term use and safety of both imidazole derivative and rifampicin in patients with *CYP24A1* mutations have not been studied. This should be the subject of future research [16]. Genetic testing is necessary to confirm the clinical diagnosis, and also for prenatal genetic counseling.

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