Case Report

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Abstract

Objectives: To emphasize the significance of genetic mutations in idiopathic infantile hypercalcemia and the potential therapeutic effectiveness of zoledronic acid in managing hypercalcemia attributed to gene mutations.

Case presentation: A 1-year-old female infant was referred to our hospital. The patient developed hypercalcemia despite no vitamin D prophylaxis or intake. In the acute phase, conventional calcium-lowering treatments showed limited efficacy, while the administration of zoledronic acid demonstrated effectiveness in controlling hypercalcemia. Subsequently the patient maintained normal calcium levels via a low-calcium diet and avoiding vitamin D intake. Genetic testing confirmed a homozygous mutation (c.476G>C) in the CYP24A1 gene.

Conclusions: Family screening and genetic counseling are crucial for early detection and prevention of hypercalcemia. This case emphasizes the importance of genetic mutations in disease development and the potential therapeutic efficacy of zoledronic acid in managing hypercalcemia attributed to gene mutations.

Keywords: bisphosphonates; CYP24A1; hypercalcemia

Introduction

Idiopathic infantile hypercalcemia (IIH) is a rare disease that affects infants and causes high levels of calcium in their blood (hypercalcemia) [1]. Hypercalcemia can lead to serious health problems, including delayed growth, vomiting, dehydration, kidney stones, low muscle tone, constipation, and delayed development.

One of the causes of IIH is a genetic mutation in the CYP24A1 gene [2], which plays a vital role in the breakdown of active vitamin D and regulates calcium levels in the body. This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monoxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids, and other lipids. This particular protein initiates the degradation process of 1,25-dihydroxyvitamin D3, which is the physiologically active form of vitamin D3, through hydroxylation of its side chain. By controlling the level of 1,25-dihydroxyvitamin D3, this enzyme significantly contributes to the regulation of calcium homeostasis and the vitamin D endocrine system [3]. When mutations occur in the CYP24A1 gene, they can impede its function, resulting in an accumulation of 1,25(OH)2D3 and subsequent disruption of calcium homeostasis.

Since 2011, researchers have identified multiple mutations in the CYP24A1 gene associated with IIH, emphasizing the significance of genetic factors in disease development [3]. These mutations can result in varying degrees of dysregulation in vitamin D metabolism and calcium balance, ultimately leading to the clinical manifestations observed in IIH patients.

The purpose of this paper is to report a newly discovered mutation in CYP24A1, describe its clinical manifestations, and explore potential treatment modalities. This newly discovered mutation in CYP24A1 was identified through genetic sequencing in a patient with suspected IIH. The patient
presented with symptoms commonly associated with IIH, including hypercalcemia, vomiting, and dehydration.

Case presentation

The patient is a one-year-old female infant and the second child of her mother’s fifth pregnancy. She was delivered through cesarean section at full term, with a birth weight of 3 kg and without any birth injuries or asphyxia. The infant was primarily breastfed with mixed formula and was introduced to complementary food at the appropriate time, but was not given prophylactic oral vitamin D. The patient was referred to our hospital due to vomiting for 3 days.

Five months before admission, the infant experienced a decrease in appetite, nausea, lack of weight gain, and constipation. Probiotics were administered but failed to improve the symptoms. Three days before admission, the patient experienced severe vomiting, polydipsia, watery stools, and reduced urine output. Physical examination revealed the infant was emaciated, had dry lips, and had little subcutaneous fat. The patient was admitted with a weight of 7 kg and a height of 75 cm. Blood tests showed elevated serum calcium levels of 3.40 mmol/L (normal range 2.25–2.75 mmol/L), indicating hypercalcemia. Serum albumin levels were 50.4 g/L, which eliminated the hypothesis that hypercalcemia was due to elevated albumin caused by acute dehydration. Additionally, the infant had elevated 25-hydroxyvitamin D levels (>70 ng/mL) but low blood phosphate (1.16 mmol/L) and low parathyroid hormone (3.9 pg/mL). A 24-h urine collection was performed, yielding a volume of 905 mL and a urinary calcium level of 2.61 mmol/L, indicating elevated urinary calcium excretion (0.37 mmol/kg). The random urine calcium to creatinine ratio was elevated (1.55 mg/mg) in the patient. Thyroid ultrasound and magnetic resonance imaging showed no abnormalities in the thyroid and parathyroid glands, nor any changes in bone structure.

Primary hyperparathyroidism and familial hypocalciuric hypercalcaemia were ruled out. The family denied any history of vitamin D use.

After the diagnosis of hypercalcemia, the infant was prescribed a low-calcium diet, and preparations containing vitamin D were prohibited. The patient received normal saline infusion, and electrolyte changes were closely monitored to avoid complications. After seven days of treatment, hypercalcemia did not improve, but there was no further aggravation.

On the 11th day of hospitalization, the infant received a single dose of zoledronic acid injection (0.175 mg) for treatment, which resulted in a decrease in blood calcium levels (Figure 1). During the hospitalization, the patient’s weight was monitored and showed no significant changes. The patient was later discharged and has since maintained normal blood calcium levels without the use of any other medication by avoiding vitamin D intake, reducing direct sunlight exposure, and adhering to a low-calcium diet. The patient’s 14-year-old brother and parents did not exhibit any abnormal symptoms (Supplementary Material Table S1).

Upon the parents’ consent, a genetic analysis was conducted and revealed a homozygous mutation in the exon region of the CYP24A1 gene: c.476G>C (p.Arg159Pro). Sanger sequencing showed that the variant was detected in the parents and the brother (Figure 2). According to the ACMG Guidelines, this mutation was classified as a likely pathogenic (PP3 strong + PM5_moderate + PM2_supporting). The variant is a novel missense change at an amino acid residue where a different missense change has been determined to be pathogenic (c.476G>A [2], PM5). No variants were found in the exome sequencing project and 1,000 genomes project databases for this query. The exome aggregation consortium database indicates an allele frequency of 0.0000159 for this variant. (PM2). The effect of the variant was evaluated using SIFT (http://sift.jcvi.org/), M-CAP (http://bejerano.stanford.edu/MCAP/), mutation assessor (http://mutationassessor.org/r3/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), mutation taster (https://www.mutationtaster.org/) to predict the pathogenic potential of the variant, which showed the pathogenic.

Discussion

This study reports a case of hypercalcemia in a Chinese patient with an unknown cause, which was eventually discovered to be caused by a homozygous mutation in the CYP24A1 gene. This gene mutation disrupts vitamin D metabolism and calcium homeostasis, making traditional treatment methods ineffective. However, treatment with zoledronic acid was eventually successful. The patient did not receive vitamin D prophylaxis or additional vitamin D intake through other means, yet still experienced hypercalcemia, indicating the crucial role of gene mutations in disease development. Zoledronic acid provides an effective treatment option for hypercalcemia patients by inhibiting bone resorption and lowering blood calcium levels, thereby avoiding potential complications such as kidney stones, renal failure, and arrhythmias. However, it is not intended to address vitamin D metabolism problems caused by patient gene mutations and is only used for acute hypercalcemia treatment.
Other authors have reported treatment options for vitamin D metabolism abnormalities, including the use of triazole drugs and rifampicin. Triazole drugs, such as ketoconazole, fluconazole [4], and itraconazole, can partially inhibit CYP27B1 and reduce the conversion of 25(OH)D₃ to 1,25(OH)₂D₃ [5, 6]. Rifampicin is a drug that induces CYP3A4 metabolism of 25(OH)D₃ and 1,25(OH)₂D₃ to 4β, 25(OH)₂D₃ and 1,23,25(OH)₃D₃, thereby improving hypercalcemia. CYP3A4 is highly expressed in the small intestine and liver and is induced by rifampicin in both tissues, replacing CYP24A1 as the degradation pathway for 1,25(OH)₂D₃ [7–9]. However, both of these drugs have side effects and require long-term use.

For individuals carrying CYP24A1 mutations, a large portion can maintain stable blood calcium levels without medication by simply avoiding vitamin D supplements, limiting sun exposure, and increasing water intake. Consequently, lifestyle modifications are essential for the long-term management of hypercalcemia. In our study, the patient we reported on was able to maintain normal blood calcium levels by following a low-calcium diet and avoiding vitamin D intake, offering a promising treatment strategy for others with similar mutations, thereby enhancing their quality of life.

Although the heterozygous relatives of the patient in this study did not develop the disease, it does not necessarily mean that the gene is in a silent state of expression. Current research indicates that IIH follows an incomplete autosomal recessive inheritance pattern, and patients carrying a single mutant allele may have mild phenotypes, manifested as clinical diseases based on environmental influences and genetic modifications [7]. Some patients have been reported to develop kidney stones, arterial calcification, and renal dysfunction in adulthood or old age [10]. Therefore, family screening and genetic counseling for hypercalcemia are crucial for the early detection and prevention of the disease. Although the patient’s relatives were asymptomatic carriers of the mutant gene and did not exhibit symptoms of hypercalcemia, we still provided them with corresponding prevention measures and suggestions, such as avoiding vitamin D intake and reduce sun exposure. Carriers of these genetic mutations showed no symptoms during follow-up.
Learning points

2. Zoledronic acid is an effective treatment for acute hypercalcemia in patients with idiopathic hypercalciuria (IHH). However, it is not designed to address the issues in vitamin D metabolism resulting from gene mutations.
3. Lifestyle interventions may play an important role in the long-term management of hypercalcemia in patients with CYP24A1 mutations.
4. Family screening and genetic counseling are crucial for the early detection and prevention of hypercalcemia.

What is new

2. Zoledronic acid as an effective therapy for acute idiopathic hypercalciuria (IHH).
3. Importance of family screening and genetic counseling in hypercalcemia prevention.

References


Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/jpem-2023-0212).