Idiopathic infantile hypercalcemia in a child presenting with failure to thrive: a case report

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Abstract

Idiopathic infantile hypercalcemia is caused by loss-of-function mutations in the *CYP24A1* gene, which encodes an enzyme that degrades vitamin D. The disease is characterized by nonspecific symptoms. In this case study, the infant merely presents with failure to thrive and dehydration, giving rise to a broad differential diagnosis. Ultrasound revealed bilateral nephrocalcinosis. Genetic research showed two compound mutations in the *CYP24A1* gene. Following a diet low in calcium and vitamin D and starting calcium-lowering therapy, led to adequate weight gain and normalized calcium levels. The case highlights the importance of determining full serum electrolytes in children with failure to thrive.

Introduction

The fat-soluble vitamin D plays a substantial role in calcium- and phosphate homeostasis (1). For this purpose, supplementation of 400-600 international units (IU) per day (depending on skin color) is routinely recommended in all newborns up to the age of 6 years (2). The degradation of active vitamin D or calcitriol is catalyzed by CYP24A1, a member of the cytochrome P450 family. Loss-of-function mutations in this enzyme cause a disease called 'idiopathic infantile hypercalcemia (IIH) type 1', which presents with nonspecific symptoms such as hypotonia, polyuria, dehydration and feeding difficulties due to hypercalcemia (1). Once diagnosed, calcium-lowering therapy should be initiated and vitamin D supplementation discontinued immediately. Caution should be taken in asymptomatic carriers, as in this case, external factors like excessive calcium or vitamin D intake may still cause late sequalae (3). We describe a case of an infant with IIH merely presenting with failure to thrive (FTT) and dehydration.

Case report

A 5-month-old girl presented to the emergency department because of poor feeding that had worsened over the past week. During this week she had fever that resolved spontaneously. According to the parents, there was no associated vomiting or diarrhea and urine production was still adequate.

There were no peculiarities in her past history. She was born at term with a normal birth weight. The infant was still exclusively breastfed at the time of presentation. Both parents were of Romanian origin, there was no consanguinity and all siblings were in good health. The infant was not receiving any medications in addition to the recommended daily dose of 400 IU of vitamin D per day.

Physical examination showed a lean and listless infant with mild signs of dehydration. There were no symptoms of infection and no syndromic stigmata. She had lost 160 grams over the past 6 weeks and the growth chart indicated that her weight had decreased 2.5 standard deviations over the previous two months.

Initial blood results revealed mild leucocytosis with normal C-reactive protein (CRP) level, acidosis, hyponatremia and hyperkaliemia. The nasopharyngeal aspirate was positive for Influenza A. Intravenous (IV) rehydration was started. On admission to the hospital, subsequent blood tests showed elevated levels of both total calcium (4,07 mmol/L, reference range 1,95-2,80 mmol/L) and free calcium (2,04 mmol/L, reference range 1,15-1,27 mmol/L). Phosphate levels were normal. Parathyroid hormone (PTH) was suppressed with a value of <6 ng/L (reference range 15-65 ng/L). 25-hydroxy vitamin D3 was markedly raised (> 100 ng/mL, reference range 10-44,8 ng/mL) with also high levels of 1,25-dihydroxy vitamin D3 (198,7 pg/mL, reference range 19-95 pg/mL). Urinalysis showed hypercalciuria with a calcium/creatinine ratio of 3,380 mg/mg (reference range <0,6 mg/mg). Renal ultrasound showed nephrocalcinosis.

The parents denied any excessive use of vitamin D supplements. No evidence of malignancy, granulomatous disease or congenital disorders was found. Genetic analysis revealed two compound heterozygous mutations in the CYP24A1 gene: c443T>C, p. (Leu148Pro) in exon 2 and c.1186C>T, p. (Arg396Trp) in exon 9.

Intravenous hyperhydration and formula low in calcium and vitamin D were started, and supplemental vitamin D was discontinued. A daily low dose of fluconazole, which can reduce the formation of 1,25-dihydroxy vitamin D3, was started. In addition, two doses of bisphosphonates were given to lower calcium levels more rapidly. Calcium and PTH levels returned to normal within three months. Feeding difficulties resolved, solid foods could be introduced, and adequate weight gain was achieved.

Discussion

Idiopathic infantile hypercalcemia was first described in the early 1950s when formula milk, heavily fortified with vitamin D, caused symptoms such as failure to thrive, vomiting, dehydration or even death in children with intrinsic hypersensitivity to vitamin D. However, it was not until 2011 that Schlingmann et al. described mutations in the CYP24A1 gene that explained this hypersensitivity (1). Later, pathogenic variants in the SLC34A1 gene, which encodes a sodium-phosphate IIa cotransporter, were found to be another molecular basis for IIH (type 2) by causing renal phosphate wasting, leading to an inappropriate increase in 1,25-dihydroxy vitamin D3 synthesis (3,4). In the presented case, both genetic mutations were investigated, although normal serum phosphate levels suggested the diagnosis of IIH type 1. The two compound loss-of-function mutations in this patient were previously described in De Paolis et al. as causing IIH type 1 (3).

The CYP24A1 enzyme catalyzes the breakdown of 1,25-dihydroxy vitamin D3 (active form) and its precursor 25-hydroxy vitamin D3 into metabolites that can be excreted (1). Low calcium levels stimulate the production of PTH which in turn downregulates CYP24A1. This process leads to an increase in concentration of active vitamin D and thus to an increase in calcium levels through intestinal absorption and renal reabsorption. In IIH type 1, loss-of-function mutations in the CYP24A1 gene prevent the breakdown of active vitamin, causing calcium levels to rise to pathological levels (3).

IIH often manifests early, usually at 3 to 7 months of age (5). Affected children may present with a variety of symptoms, including vomiting, polyuria, dehydration, anorexia, constipation and weight loss. Lethargy and muscular hypotonia may also occur (3,5,6). Sometimes, the disease can be accompanied by seizures, pancreatitis or psychiatric symptoms (6). Our patient presented with failure to thrive, which is described in about three quarters of the cases reported in literature (7). If the initial symptoms go undetected, other problems such as kidney stones, renal failure, osteoporosis or calcium deposition in the cornea or joints may develop. Patients who are carrier of a mutation may also show these latent symptoms, mainly when vitamin D is taken in excess (3,5).

Typical laboratory findings are hypercalcemia, hypercalciuria and supressed PTH levels (3). 1,25-dihydroxy vitamin D3 is usually slightly elevated but tends to normalize due to downregulation by PTH (5). Another diagnostic clue is an elevated ratio of serum 25-hydroxy vitamin D3 to its catabolite 24,25-dihydroxy vitamin D3 (5,8). In some patients, abdominal ultrasound may reveal nephrocalcinosis (1).

Failure to thrive can be caused by a wide range of conditions. The finding of PTH-independent hypercalcemia with normal to high calcitriol levels suggests the possible diagnosis. In children, congenital causes, such as IIH types 1 and 2, are more common than acquired etiologies. Early onset of the condition, consanguinity, a family history of hypercalcemia or a history of multiple or recurrent kidney stones, should raise the suspicion of a genetic disorder (3). Some congenital syndromes associated with hypercalcemia, such as William syndrome, Down syndrome, and Jansen disease, can be identified by dysmorphic features (6,8). PTH-independent hypercalcemia may also be seen in some rare inborn errors of metabolism such as blue diaper syndrome, hypophosphatasia, congenital lactase deficiency or disaccharide intolerance (6). Among the acquired disorders, (accidental) intoxication with vitamin D, vitamin A or some drugs should be considered first (6). Extrarenal overproduction of vitamin D occurs in granulomatous disorders or malignancies such as lymphoma or ovarian dysgerminoma. In neonates, subcutaneous fat necrosis is a rare and reversible cause of hypercalcemia, caused by the formation of a granulomatous infiltrate in the necrotic area (6,8).

Children diagnosed with IIH require prompt treatment. Hyperhydration with or without loop diuretics will stimulate calcium excretion and rapidly reduce calcium levels. A diet low in calcium and vitamin D has to be prescribed (3,8). In the next phase of treatment, a more prolonged reduction of calcium levels should be achieved. Several options have been explored, including the use of corticosteroids, especially for hypercalcemia due to granulomatous disease, or the use of calcitonin, although its effect is short-lived (3,6). A 2- to 3-day course of bisphosphonates can be given to inhibit osteoclast activity and thereby lowering calcium levels. This course can be repeated every 6 to 8 weeks (3,6). In addition, azole antifungals are known to be general inhibitors of the cytochrome P450 complex. Consequently, they also interfere with the function of the 25-hydroxylase and 1-alpha-hydroxylase enzymes, thereby reducing the production of vitamin D. Ketoconazole is a more potent inhibitor with a higher risk of hepatic and renal toxicity than the more readily available fluconazole (3,5,9). Rifampicin is an inducer of the CYP3A4 enzyme, which could act as different approach to break down vitamin D (6). It is important that these medications are gradually reduced as calcium levels normalize (5).

In the literature little is known about the natural course and prognosis of IIH. According to some studies hypercalcemia resolves spontaneously in most children at the age of one to three years. In a small number of patients, suboptimal calcium levels persist into adulthood (5,6). Long-term adverse outcomes have been reported, including mild to moderate intellectual disability, anxiety and hyperactivity (5). The implications on bone development also remain unclear, as both low, normal and high bone mineral density have been described (8). In the presented case, the patient showed a rapid catch-up growth after initiation of diet and calcium-lowering therapy. Treatment with fluconazole could be weaned after approximately three months.

Conclusion

When a child presents with failure to thrive, hypercalcemia needs to be excluded by performing a complete serum electrolyte panel during the diagnostic evaluation. A genetic cause of hypercalcemia should be considered in the presence of early onset of disease or conspicuous family or medical history. In these cases, IIH should be considered in the differential diagnosis. High-dose vitamin D supplementation should be used with caution, as it may endanger children with *CYP24A1* mutations. Finally, more research is needed on the natural course and the long-term impact of IIH.

Conflict of interest

All authors declare that they have no conflict of interest in relation to the realization of this case report.

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