Intravenous Pamidronate in the Treatment of Severe Idiopathic Infantile Hypercalcemia

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Idiopathic infantile hypercalcemia (IIH) is a rare disorder caused by *CYP24A1* loss-of-function mutation, resulting in impaired degradation of 1,25-dihydroxyvitamin D3. Pamidronate, an intravenously administered bisphosphonate, which is a potent inhibitor of bone resorption, has been reported only once for treatment IIH. We present a case of a previously healthy 5-month-old boy with IIH, where calcemia peaked to 5 mmol/L. Treatment with methylprednisone and furosemide had only minor effects; therefore, 2 intravenous infusions of pamidronate (0.6 mg/kg per dose) corrected the serum calcium level to 2.95 mmol/L. Furthermore, *CYP24A1* homozygous mutation p.R396W (c.1186c>t) was identified in this patient, confirming the clinical diagnosis of IIH. In conclusion, IIH has a favorable outcome once properly detected and appropriately treated. Pamidronate has a beneficial effect in those patients with IIH where glucocorticoids and furosemide fail to meet the expectations.

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Case Report

INTRODUCTION

Idiopathic infantile hypercalcemia (IIH) is a rare disorder occurring in the first year of life. Idiopathic infantile hypercalcemia is caused by *CYP24A1* mutation, resulting in slow inactivation of 1,25-dihydroxyvitamin D3 with subsequent hypercalcemia.[1] Typical signs include lethargy, muscle hypotonia, dehydration, fever, failure to thrive, psychomotor retardation, constipation, and nephrocalcinosis.[1-3] Idiopathic infantile hypercalcemia should be distinguished from other causes of hypercalcemia in infancy, such as Williams-Beuren syndrome, neonatal severe primary hyperparathyroidism, benign familial hypocalciuric hypercalcemia, primary hyperparathyroidism, Jansen metaphyseal dysplasia, granulomatous diseases, subcutaneous fat necrosis, and vitamin D intoxication (Table).[2-5] Treatment includes low calcium diet, glucocorticoids, furosemide, phosphate, and eventually calcitonin. We present a patient with severe IIH, where pamidronate was applied and had a beneficial effect.

CASE REPORT

A 4.5-month-old boy of unrelated parents with uneventful family and neonatal history (full term; birth weight, 4350 g; birth height, 54 cm) and no dysmorphic signs was referred because of poor apetite, dehydration, constipation (stool frequency once a week), and failure to thrive. His weight had dropped from 7010 g at the age of 3 months (+ 0.7 SD) to 6410 g at month 4 (-0.8 SD). He was breastfed and receiving 666 units of cholecalciferol per day as antirachitic prophylaxis and he had never received a higher dose of vitamin D.

At a district healthcare facility, he underwent intravenous rehydration and was initially treated for urinary tract infection, suggested by fever, leukocytosis (22.9 × 10^9/L and 31.3 × 10^9/L) and leukocyturia, for 4 days with intravenous

Differential Diagnosis of Hypercalcaemia Throughout the First Year of Life

Disorder	Cause	Blood studies					Urine Studies	
		Calcium	Phosphate	Parathyroid Hormone	25-Hydroxyvitamin D3	1,25-Hydroxyvitamin D	Calcium	Phosphate
Idiopthic infantile hypercalcaemia	CYP24A1 mutation	High	Normal	Low	Normal to high	Normal to high	High	Normal
Williams-Beuren syndrome	Elastin gene deletion	High in 15%	Normal to high	Low	Normal	Normal to high	High in 30%	Normal
Neonatal severe hyperparathyroidism	CASR homozygous inactivating mutation	Very high	Low	High	Normal to low	High	High	Normal to high
Familial hypocalciuric hypercalcaemia	CASR heterozygous inactivating mutation	Normal to high	Normal to low	Normal to high	Normal	High	Low	Normal to high
Jansen metaphyseal dysplasia	PTH receptor activating mutation	High	Low	Normal	Normal	High	High	High
Primary hyperparathyroidism	Increased parathyroid hormone secretion	High	Low	High	Normal	High	High	High
Vitamin D overdose	High vitamin D intake	High	High	Low	High	Normal	High	High
Subcutaneous fat necrosis	High calcitriol production	High	High	Low	Normal	Very high	High	High
Granulomatous disease	High calcitriol production	High	High	Low	Normal	Very high	High	High
Malignancy	Humoral or osteolytic malignancy	High	Low (humoral) High (osteolytic)	Low	Normal	High (humoral) Low (osteolytic)	Normal or high	High

ampicillin/sulbactam. Further laboratory evaluation revealed high total serum calcium (4.96 mmol/L; reference range, 2.2 mmol/L to 2.7 mmol/L) and serum ionized calcium (1.99 mmol/L; reference range, 1.1 mmol/L to 1.3 mmol/L), high urinary calcium excretion (0.37 mmol/kg/24 h; reference range, 0.03 mmol/kg/24 h to 0.09 mmol/kg/24 h), and high urinary calcium-creatinine ratio (4.7; reference range, < 1.5). The following parameters were in normal range: serum concentrations of sodium, chloride, potassium, phosphorus, magnesium, bilirubin, aspartate aminotransferase, and alanine aminotransferase, as well as serum osmolality. Serum alkaline phosphatase activity was low (1.17 µkat/L; reference range, 2.5 µkat/L to 6.0 µkat/L).

The patients was transferred to a tertiary healthcare facility. Upon admission his serum calcium was 4.45 mmol/L, serum ionized calcium was 2.19 mmol/L, serum phosphate was 1.12 mmol/L (reference range, 1.3 mmol/L to 2.3 mmol/L). The levels of serum protein and albumin were elevated and leukocytosis persisted, all due to dehydration. The urinary calcium-creatinine ratio was high (3.2). Bacteriuria was not present. The serum levels of free thyroxine and thyrotropin were normal. His serum parathyroid hormone was very low (1 pg/mL; reference range, 10 pg/mL to 50 pg/mL). The serum level of calcidiol (25-hydroxyvitamin D3) was high (180 nmol/L; reference range, 23 nmol/L to 113 nmol/L).

Nephrocalcinosis and gallbladder calcification were apparent on abdominal ultrasonography. Tc-99m Technetium bone scan was normal. Echocardiography revealed small, hemodynamically nonsignificant atrial septal defect and no signs of aortal or pulmonary artery stenosis. The American Academy of Pediatrics Committee on Genetics Score for Williams-Beuren syndrome[6] was 3 points; thus ruling out this disorder. Radiography of the left hand showed dense bone, without any signs of Jansen metaphyseal dysplasia. Hypercalcemia with hypercalciuria, suppressed serum parathyroid hormone, low Williams-Beuren syndrome score, normal thyroid function, no signs of granulomatous disease or subcutaneous fat necrosis, absense of Jansen metaphyseal dysplasia signs, and a negative history of vitamin D overdosage pointed to the very rare diagnosis of IIH.

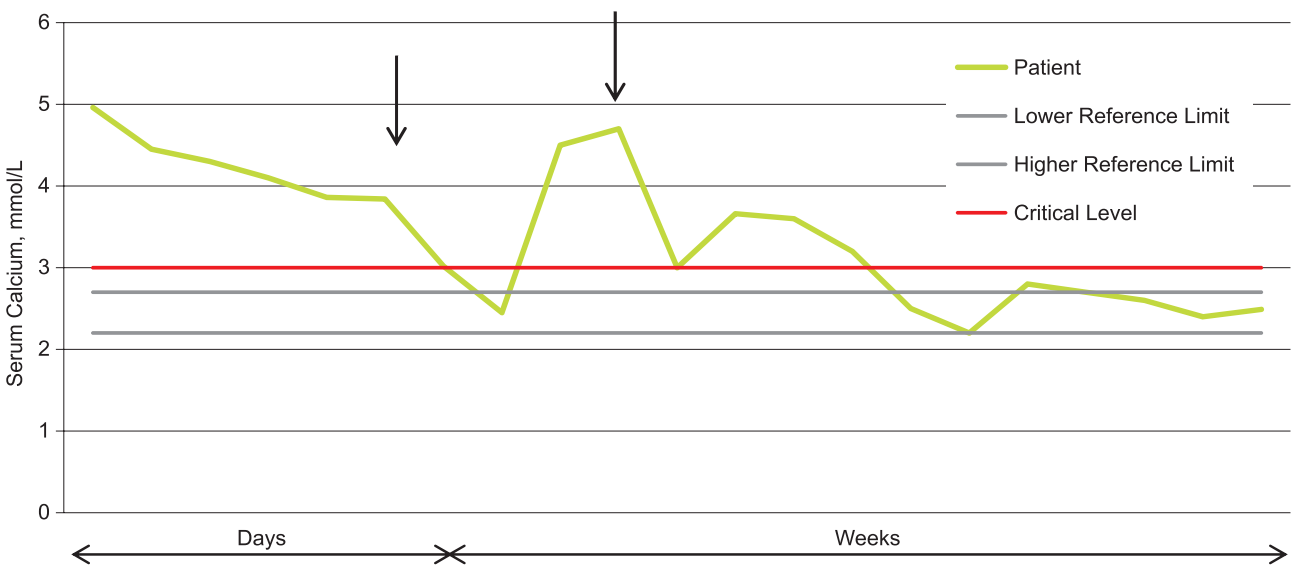
The patient was maintained on rehydration

therapy with 0.9% and 0.45% saline solution, respectively, and was also started on intravenous glucocorticoids (methylprednisone, 1.5 mg/kg/d) and furosemide (1.5 mg/kg/d). Prophylactic vitamin D application was stopped immediately. After 4 days of treatment serum albumin, protein, and creatinine levels reached normal values as a result of rehydration. His blood count normalized. At the same time the total serum calcium dropped to 3.86 mmol/L, and persisted at 3.84 mmol/L the following day (Figure). Therefore, a single infusion of intravenous pamidronate (0.6 mg/kg) was applied, which resulted in a decrease of serum calcium level to 3.07 mmol/L within the next 24 hours (Figure). The urinary calcium concentration dropped to 0.07 mmol/kg/24 h and urinary calcium-creatinine ratio to 1.32. There was no febrile or flu-like reaction after the pamidronate application. The child was discharged after additional 10 days with a serum calcium level of 2.44 mmol/L and followed on an outpatient basis, receiving furosemide (1 mg/kg/d), prednisone (1.5 mg/kg/d), and phosphate solution (50 mg of phosphorus per kg/d).

One week later, there was a recurrence of hypercalcemia (4.49 mmol/L and 4.64 mmol/L, respectively), refractory to furosemide and prednisone. The patient was re-admitted and received another infusion of pamidronate (4 mg). Afterwards, serum calcium level gradually decreased to 2.95 mmol/L (Figure). The urinary calcium-creatinine ratio dropped from 1.86 to 0.44. The patient was discharged after 1 week and followed for 10 weeks on a weekly basis. After the discharge, serum calcium level increased to 3.66 mmol/L. In the course of the following 6 weeks, the boy was maintained on furosemide (0.7 mg/kg/d) and on phosphate (50 mg/kg/d) as his serum calcium level gradualy dropped to 2.39 mmol/L. Furosemide was stopped and he received phosphate for an additional 4 weeks and at that time his serum calcium level reached 2.2 mmol/L and remained within the normal reference range afterwards.

On the latest visit, the child was 3.5 years old, obese, and was being followed on an outpatient basis. There were no signs of psychomotor retardation or developmental delay. His body weight was 21.5 kg (+3 SD), body height wais 96 cm (-0.8 SD), and body mass index was 23.3 kg/m^2 (+5.2 SD). The serum calcium level was normal (2.49 mmol/L), same as serum phosphate (1.6 mmol/L), alkaline phosphatase (3.15 µkat/L), and urinary calcium/-creatinine ratio (0.46 mmol/L:mmol/L). Serum parathyroid hormone was slightly subnormal (8.9 pg/mL). Nephrocalcinosis still persisted with otherwise normal creatinine clearance.

Furthermore, genetic testing was performed (at the Department of Pediatric Nephrology, University Children´s Hospital, Muenster, Germany), and *CYP24A1* homozygous mutation p.R396W (c.1186c>t) was identified, confirming the



Course of serum calcium changes in the patient. Vertical arrows indicate the administration of pamidronate.

clinical diagnosis of IIH. Serum levels of calcium, phosphate, alakaline phoshatase, and parathyroid hormone were within normal reference ranges in his parents and sister.

DISCUSSION

Idiopathic infantile hypercalcemia (Online Mendelian Inheritance in Man OMIM #143880) is a rare cause of hypercalcemia in the first year of life with an estimated incidence of approximately 1 in 47 000 live births. Idiopathic infantile hypercalcemia was originally described in England in the 1952 as a result of high-dose vitamin D fortification and in Switzerland.[67,8] The cause of IIH was unknown for several decades and an increased sensitivity to vitamin D or slow or impaired elimination of vitamin D and its metabolites had been suggested.[2,9,10] This was supported by the observation that IIH was triggered by administration of high vitamin D doses, or even by vitamin D antirachitic prophylaxis of 500 IU/d.[1,2,7,11,-13] The relationship of IIH with mutations in claudin (*CLDN*) 3 and 4 genes had been also proposed and subsequently ruled out.[11]

Just recently, in 2011, loss-of-function mutations in *CYP24A1* gene, which is located at 20q13 and encodes 25-hydroxyvitamin D 24-hydroxylase, the key enzyme of 1,25-dihydroxyvitamin D3 degradation, were identified in IIH patients where either hypercalcemia occurred after vitamin D prophylaxis (500 IU/d) or severe hypercalcemia had developed after bolus prophylaxis with vitamin D.[1] The presence of *CYP24A1* mutations most likely explains the increased sensitivity to vitamin D in patients with IIH and is a genetic risk factor for the development of symptomatic hypercalcemia that may be triggered by vitamin D prophylaxis in otherwise apparently healthy infants, as was the case in our patient. Idiopathic infantile hypercalcemia is inherited as an autosomal recessive trait.[1]

In general, untreated hypercalcemia leads to soft tissue calcification, including urolithiasis and nephrocalcinosis, and to osteosclerosis.[4,5] In IIH, the hypercalcemia can persist up to 2 years of age, while nephrocalcinosis persists occassionally up to 12 years.[3,14,15] Urinary tract infection might occur in the presence of hypercalciuria.[13,14] Prompt treatment is necessary in patients with serum calcium level of 3.0 mmol/L accompanied by clinical symptoms, and in all patients with serum calcium levels of 3.5 mmol/L and greater, as hypercalcemia exceeding 3.5 mmol/L can result in cardiac arrest.[4,16]

The course of IIH is variable, as it can be sometimes easily managed by brief application of corticosteroids or furosemide, and on other occassions, a prolonged treatment lasting for several weeks is necessary. Pamidronate, an intravenous nitrogen-containing bisphosphonate, which is a potent inhibitor of bone resorption, is used to treat hypercalcemia of malignancy, Paget disease of bone, and osteolytic bone metastases and lesions. Due to its strong antiresorptive properties, pamidronate is a very effective agent in lowering serum calcium level.[4,16] Concerning pediatrics, pamidronate is an off-label drug and has been so far used only in infants with osteogenesis imperfecta,[13, 5-7] and individually in infants with hypercalcemia due to Williams-Beuren syndrome,[18] acute leukemia,[19] and neonatal severe hyperparathyroidism.[2,5,20] There is one brief mention of pamidronate in the treatment of a patient with IIH.[1] Therefore, the clinical experience with pamidronate in infants with hypercalcemia is rather scarce. To date, rehydration, corticosteroids, furosemide, and phosphate cellulose have been effective in the management of IIH.[2,12,13] Recently, ketoconazole was also reported to be effective in IIH.[21] As our patient had hypercalcemia with hypercalciuria, low serum parathyroid hormone level, low Williams-Beuren syndrome score, the clinical diagnosis of IIH was established since there was no signs of metaphyseal dysplasia on radiography, no history of vitamin D overdose, and no signs of malignancy, thyroid disease, or subcutaneous fat necrosis. This was later confirmed by the finding of homozygous mutation R396W. Such a mutation has been identified before in other IIH patients and has been shown to functionally result in a complete loss-of-function of the encoded *CYP24A1* protein.[1]

Application of pamidronate in our patient was considered as inevitable, due to refractory hypercalcemia and all its possible grave consequences. The necessity of second pamidronate infusion clearly illustrates the unpredictable course of IIH. In conclusion, pamidronate should be considered an effective drug in severe cases of IIH, where corticotherapy and furosemide have only little effects. Once properly detected and appropriately treated, IIH has a favorable outcome.

CONFLICT OF INTEREST

None declared.

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