Successful Use of Bisphosphonate and Calcimimetic in Neonatal Severe Primary Hyperparathyroidism

abstract

Neonatal primary hyperparathyroidism (NPHT) is associated with an inactivating homozygous mutation of the calcium sensing receptor (CaSR). The CaSR is expressed most abundantly in the parathyroid glands and the kidney and regulates calcium homeostasis through its ability to modulate parathormone secretion and renal calcium reabsorption. NPHT leads to life threatening hypercalcemia, nephrocalcinosis, bone demineralization, and neurologic disabilities. Surgery is the treatment of choice. While waiting for surgery, bisphosphonates offer a good alternative to deal with hypercalcemia. Cinacalcet is a class II calcimimetic that increases CaSR affinity for calcium, leading to parathormone suppression and increased calcium renal excretion. At present, there is little evidence as to whether cinacalcet could improve the function of mutant CaSR in NPHT. We report a case of NPHT, treated successfully with bisphosphonates and cinacalcet after surgery failure. To our knowledge, it is the first time cinacalcet has been used for NPHT. *Pediatrics* 2012;129:e812–e816

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KEY WORDS

neonatal primary hyperparathyroidism, parathormone, calcium sensing receptor, calcimimetic of class II

ABBREVIATIONS

BMD—bone mineral density
CaSR—calcium sensing receptor
NPHT—neonatal primary hyperparathyroidism
PTH—parathormone

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Neonatal primary hyperparathyroidism (NPHT) is a rare autosomal dominant disease associated with an inactivating homozygous mutation of the calcium sensing receptor (CaSR). NPHT appears within the first months of life with severe symptomatic hypercalcemia, polyuria, failure to thrive, hypotonia, respiratory distress, bone deformity, and fractures. If untreated, NPHT can be a devastating neurodevelopmental disorder and is often fatal.[1–4]

CaSR is expressed in several tissues and acts as a "calciostat," sensing serum calcium level. In the parathyroid gland, the activation of CaSR modulates parathormone (PTH) synthesis and secretion.

In the kidney, CaSR is expressed in all nephron segments. Depending on the localization, CaSR has an inhibitory effect on the reabsorption of calcium, potassium, sodium, and water.[5]

CaSR receptor has been identified in other tissues, including calcitonin cells, gut, skeleton, and brain, where its function and physiologic importance remain to be explained.[3]

In NPHT, surgery is the treatment of choice and is effective in most cases.[6] As an alternative to surgery, bisphosphonates have been shown to be efficient in handling hypercalcemia.[7,8] Cinacalcet increases CaSR affinity for calcium leading to diminished PTH secretion and increased renal calcium excretion. Little is known about the use of cinacalcet in NPHT to improve the function of mutant CaSR. We report the case of a girl diagnosed at birth with NPHT and treated successfully with bisphosphonates and cinacalcet after surgery had failed.

CASE REPORT

The patient presented in the first week of life with poor feeding, lethargy, and apnea. The laboratory tests revealed: hypercalcemia 8.25 mmol/L (reference range: 2.20–2.52 mmol/L) and hyperparathyroidism 95.4 pmol/L (reference range: 1.2–6.4 pmol/L). The family history, pregnancy, and birth were uneventful. Serum calcium and PTH levels were normal in both parents. The brother of the patient was asymptomatic, had normal blood calcium, slightly increased PTH, and decreased calciuria on a urinary spot analysis. He was genetically tested and is a heterozygous carrier.

When the patient was 1 month old (December 1999), 4 parathyroid glands were removed, 1 of which was transplanted into the left arm (5 implants along a longitudinal line in the deltoid muscle). Histologic examination confirmed primary hyperparathyroidism caused by chief cell hyperplasia.

Postoperatively, PTH and calcium levels remained high (30 pmol/L and 6 mmol/L, respectively). The left arm implant was removed, but the patient continued to have abnormal values. Between January 2001 and February 2002, sestamibi ^{99m}Tc scanning, MRI, and venous sampling of PTH showed suspected focus of residual PTH secretion in the anterior mediastinum and on both arms (Fig 1). The patient underwent 6 interventions, none of which detected residual parathyroid tissue. The hypothesis to explain the persistence of hyperparathyroidism was a miliary spread of the parathyroid cells.

At that time, under a hyperhydration regimen but with a normal calcium diet, laboratory results were as follows: calcium 5 mmol/L, PTH 25 to 30 pmol/L, phosphate 0.7 mmol/L (reference range: 1.20–1.9 mmol/L), 25-OH-cholecalciferol 50 nmol/L (reference range: 20–90 nmol/L), urinary calcium/creatinine ratio 0.1 (reference range: <0.7). Bone turnover markers: urinary molar fraction deoxypridinoline/creatinine 382.3 (reference range: 8–20.2), serum osteocalcin: 108 μg/L (reference range for gender and age: 48–79 μg/L), alkaline phosphatase 490 U/L (reference range: 120–360 U/L).[9] The creatinine clearance (April 2001) was 100 mL/min $\times$ 1.73 m^2. The renal ultrasound (December 2000) showed

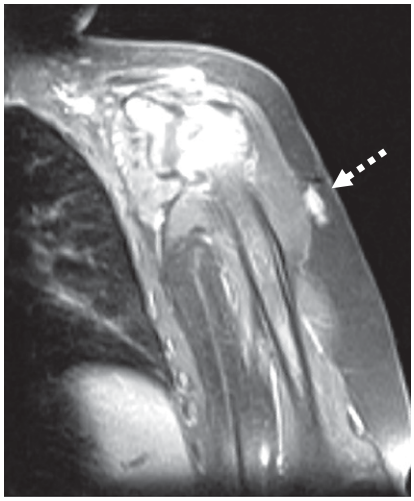

FIGURE 1
MRI (Fat saturation T1+ gadolinium April 2001) of the left arm showing (arrow) a suspected focus of residual parathyroid tissue.

nephrocalcinosis. The bone mineral density (BMD) of the spine L2 to L4 (dual-energy x-ray absorptiometry, DXA realized on Hologic QDR-4500A s/n 45278 [Hologic, Switzerland]) showed a low z score adjusted for gender and age (-2.2).

The child did not present with fractures or bone deformity on physical examination. Staturoponderal growth was -2 SD for weight and height, and the patient developed psychomotor retardation mainly in motor acquisition.

At age 2 years, treatment with bisphosphonates was initiated. The patient benefited from pamidronate infusion (1 mg/kg per day over 3 days) every 4 months between December 2001 and November 2005. Supplementation with vitamin D (cholecalciferol 400 UI/day) and sodium phosphate (1 mmol/kg per day) was also initiated.

Calcium decreased to 3 mmol/L, PTH decreased to 10 pmol/L. The other laboratory values changed as follows: phosphate 0.9 mmol/L, 25-OH-cholecalciferol 102 nmol/L, urinary calcium/creatinine ratio 0.1. Bone turnover markers: urinary molar fraction deoxypridinoline/creatinine 71, serum osteocalcin: 51 μg/L (reference range for gender and age: 65–96 μg/L), alkaline phosphatase 230

U/L. The BMD of the spine L2 to L4 (November 2004) showed an improved *z* score at 1.3. Finally, nephrocalcinosis on the renal ultrasound decreased.

The patient did much better, and we observed an improvement of psychomotor delay and staturoponderal growth (−1 SD).

At age 6 years (May 2006), a trial with cinacalcet was started with a first dose of 30 mg, which was increased to 90 mg and 60 mg a day on alternating days (July 2006). With this treatment, calcium level decreased to 2.6 mmol/L, and PTH lowered to 5 pmol/L (Fig 2). The other laboratory results changed as follows: phosphate 1.14 mmol/L, 25-OH-cholecalciferol 76 nmol/L, urinary calcium/creatinine ratio 0.2, bone turnover markers: serum osteocalcin 80 μg/L (reference range for gender and age: 65–96 μg/L), alkaline phosphatase 214 U/L. Under cinacalcet, the patient growth continued to follow the −1 SD, and no other secondary effects were observed. In 2010, calcium increased to 2.8 mmol/L and PTH to 5.5 mmol/L, and we increased cinacalcet to 90 mg per day with a good results; calcium decreased to 2.6 mmol/L and PTH to 4.6 pmol/L.

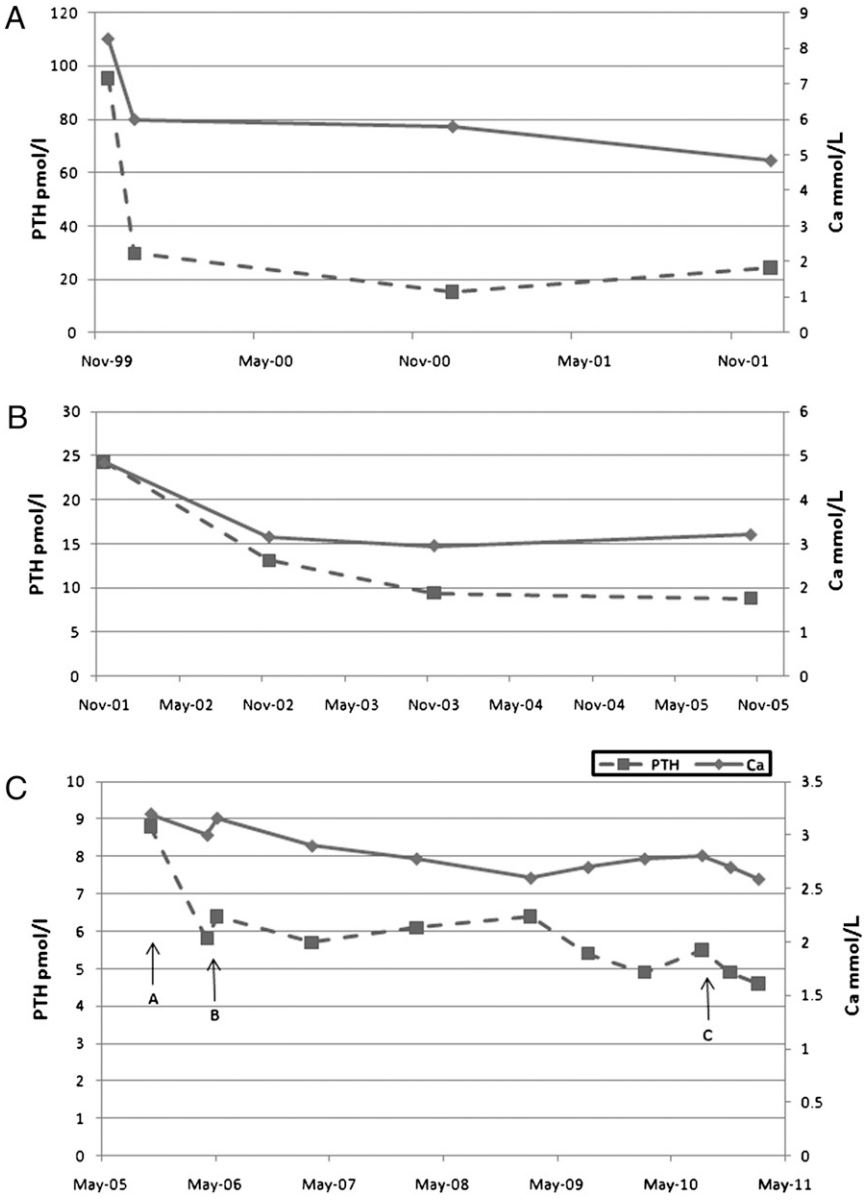

FIGURE 2

A, Diminution of calcium and PTH after surgery. B, Diminution of calcium and PTH under bisphosphonates therapy. C, Normalization of calcium and PTH under cinacalcet therapy. Arrow A, cinacalcet 30 mg/d; arrow B, cinacalcet 60 mg/d and 90 mg/d on alternate days; arrow C: cinacalcet 90 mg/d. Calcium reference range: 2.20 to 2.52 mmol/L; PTH reference range: 1.2 to 6.4 pmol/L.

These examinations were done at the university hospital of Limoges by Drs Sturtz and Magdelaine. The molecular biology demonstrated a homozygous mutation in the third exon of the *CasR* gene. This mutation (c.206G>A) has never been described before and is characterized by the replacement of an arginine by a histidine in position 69 in the extracellular domain of the protein. Each parent carries the mutation in a heterozygous state. In vitro activity of the mutation is currently being tested.

DISCUSSION

Although surgery is currently the only curative treatment for NPHT, our patient had residual parathyroid tissue. As an alternative, we started treatment with bisphosphonates. Under bisphosphonates, as expected, we observed an improvement of calcium level. The BMD normalized and the bone turnover markers improved. Statural growth increased, and the patient's psychomotor skills improved. We also noticed an unexpected diminution of PTH from 20 pmol/L to 10 pmol/L, which was not completely understood. Usually, bisphosphonates induce a fall in blood calcemia and an additional increase in PTH. This unexpected fall in PTH level might represent a natural evolution of the disease.[7] It might also result from a different bone metabolism under treatment, but the mechanism remains unclear. CaSR is expressed in the bone, but no link between bone CaSR and parathyroid gland regulation has been

described. Fibroblast growth factor 23 is also secreted in the bone and is known to decrease PTH secretion; however, recent articles showed that pamidronate induces a fall in fibroblast growth factor 23 secretion.[10] Interestingly, another case of NPHT treated with pamidronate, described by Waller et al,[7] showed a similar fall in PTH but a rebound 2 months later. In this case, however, only 1 dose of pamidronate was given.

Our patient stayed on bisphosphonates for >3 years, and we did not notice any secondary effects. In particular, growth improved, and long bone radiographs were normal apart from the bisphosphonate-induced transverse sclerotic lines, but there were no changes suggestive of osteopetrosis. Because adverse effects from long-term treatment with bisphosphonates are largely unknown, we decided to stop the bisphosphonates treatment and initiate cinacalcet therapy.[11]

The half-life of bisphosphonates in the skeleton is long because it is incorporated in the bone and released during bone remodeling. It has been demonstrated that the effect of bisphosphonates on bone density can be sustained for 26 ± 2 months after discontinuation in children.[12] In our case, cinacalcet was started shortly after bisphosphonates discontinuation, and the initial results observed on hypercalcemia may be, in part, due to the remaining effects of the bisphosphonates therapy.

Cinacalcet was started at 30 mg per day (1.4 mg/kg per day) and increased to 3.5 mg/kg per day while monitoring the impact on PTH and calcium level because no standard therapy was available for this condition. Under therapy with cinacalcet, we observed normalization of PTH and phosphate and near normalization of calcium, suggesting a positive effect of the calcimimetic on the mutant CaSR in the parathyroid gland.

In the kidney, the activation of CaSR leads to an increase in calcium excretion directly through a diminished paracellular passive reabsorption in the thick ascending loop of Henle and indirectly through a diminution of PTH. In our patient, calciuria did not increase after the initiation of treatment and stayed low compared with the value of serum calcium.

In the bone, CaSR is present in the osteoblasts and the growth plate. Both in vitro and in vivo data indicate a role of CaSR in osteoblast and osteoclast recruitment, differentiation, and survival. In mice experiments, tissue-specific deletion of CaSR in osteoblasts resulted in profound bone defects, whereas CaSR deletion in chondrocytes resulted in delayed growth plate development.[13,14]

Calcimimetics exert an indirect effect on bone via modulation of PTH. Direct effects of calcimimetic targeting bone CaSR is difficult to predict. In our patient, we did not observe any adverse effect on bone metabolism of the treatment. On the contrary, bone turnover markers stayed in the normal range for age and gender, and growth followed the same percentile (−1 SD). A bone age assessment, according to Greulich and Pyle, was performed both while receiving bisphosphonates and later cinacalcet. It showed a delay of 1 year between chronological age and bone age, which was not modified by the introduction of cinacalcet.

On follow-up, 6 years after the bisphosphonates were discontinued, calcium and PTH are stable under cinacalcet alone. When cinacalcet was introduced, the patient felt much better without any adverse secondary effect at 6 years' follow-up. In 2010, calcium increased to 2.8 mmol/L and PTH to 5.5 pmol/L, and we decided to increase the cinacalcet further to 90 mg each day with a good response; calcium decreased to 2.6 mmol/L, and PTH decreased to 4.6 pmol/L. Although a natural amelioration of the severity of the disease was possible, we were not willing to try a drug holiday.

Currently, little is known about the use of calcimimetics in NPHT. Rus et al[15] characterized in vitro 7 mutations of the CasR in familial benign hypocalciuric hypercalcemic patients. They showed that NPS R-568, an analog of cinacalcet, improves the signal of the mutant CasR in 4 cases out of 7. A recently published case report also describes a normalization of PTH and calcium under cinacalcet in a child with familial benign hypocalciuric hypercalcemia.[16]

In our patient, a mutation was found in the extracellular domain with the replacement of an arginine by a histidine. This mutation should not change the chemical characteristics of the region (electrical charge, hydrophobicity), but it could modify the steric shape of the extracellular domain, leading to calcium-binding difficulties.

In this mutation, cinacalcet seemed to be successful and was able to normalize PTH and calcium serum levels. More than 200 mutations of the CaSR are described in NPHT, and it is difficult to predict which will respond to cinacalcet therapy. However, it seems reasonable and worth trying as an alternative to surgery or while waiting for surgery.

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