Successful treatment of neonatal severe hyperparathyroidism with cinacalcet in two patients

Marisa M Fisher¹, Susanne M Cabrera² and Erik A Imel¹,³

¹Division of Pediatric Endocrinology, Department of Pediatrics, Riley Hospital for Children, Indiana University School of Medicine, 705 Riley Hospital Drive, Room 5960, Indianapolis, Indiana 46220, USA
²Division of Pediatric Endocrinology, Department of Pediatrics, Medical College of Wisconsin, Children’s Hospital of Wisconsin, 9000 W. Wisconsin Avenue, PO Box 1997, Milwaukee, Wisconsin 53201, USA
³Division of Endocrinology, Department of Medicine, Indiana University School of Medicine, 541 North Clinical Drive, Indianapolis, Indiana 46202, USA

Correspondence should be addressed to M M Fisher
Email mamfishe@iu.edu

Summary

Neonatal severe hyperparathyroidism (NSHPT) is a rare disorder caused by inactivating calcium-sensing receptor (CASR) mutations that result in life-threatening hypercalcemia and metabolic bone disease. Until recently, therapy has been surgical parathyroidectomy. Three previous case reports have shown successful medical management of NSHPT with cinacalcet. Here we present the detailed description of two unrelated patients with NSHPT due to heterozygous R185Q CASR mutations. Patient 1 was diagnosed at 11 months of age and had developmental delays, dysphagia, bell-shaped chest, and periosteal bone reactions. Patient 2 was diagnosed at 1 month of age and had failure to thrive, osteopenia, and multiple rib fractures. Cinacalcet was initiated at 13 months of age in patient 1, and at 4 months of age in patient 2. We have successfully normalized their parathyroid hormone and alkaline phosphatase levels. Despite the continuance of mild hypercalcemia (11–12 mg/dl), both patients showed no hypercalcemic symptoms. Importantly, patient 1 had improved neurodevelopment and patient 2 never experienced any developmental delays after starting cinacalcet. Neither experienced fractures after starting cinacalcet. Both have been successfully managed long-term without any significant adverse events. These cases expand the current literature of cinacalcet use in NSHPT to five successful reported cases. We propose that cinacalcet may be considered as an option for treating the severe hypercalcemia and metabolic bone disease found in infants and children with inactivating CASR disorders.

Learning points:

- NSHPT due to mutations in the CASR gene occurs with hypercalcemia and metabolic bone disease, but not always with severe critical illness in infancy.
- NSHPT should be considered in the differential diagnosis for a newborn with a bell-shaped chest, osteopenia, and periosteal reactions.
- Neurodevelopmental consequences may occur in children with hypercalcemia and may improve during treatment.
- Calcimimetics can be used to successfully treat the pathophysiology of NSHPT directly to control serum calcium levels.
Background

The calcium-sensing receptor (CASR) is a 1078 amino acid cell surface protein with a large extracellular domain that tightly regulates calcium homeostasis (1). Under normal conditions, increasing extracellular calcium concentrations activate the CASR, diminishing parathyroid hormone (PTH) release and augmenting renal calcium excretion (2). Inactivating CASR gene mutations lead to variable degrees of hypercalcemia. Heterozygous mutations usually result in mild hypercalcemia seen in familial hypocalciuric hypercalcemia (FHH). Homozygous CASR mutations result in neonatal severe hyperparathyroidism (NSHPT), producing life-threatening hypercalcemia and extreme PTH and alkaline phosphatase elevations in the neonatal period. Patients usually present in the first weeks of life with failure to thrive, hypotonia, respiratory distress, and metabolic bone disease. Bone abnormalities can include undermineralization, rib cage deformities, subperiosteal erosions, metaphyseal widening of the long bones, and fractures (1).

Heterozygous CASR gene mutations resulting in the NSHPT phenotype have also been described (3) (4) (5). The heterozygous mutation, R185Q, is one such mutation and in vitro studies have demonstrated the dominant negative inhibition of the WT CASR by this mutant CASR (4) (6). Until recently, the only effective therapy for NSHPT was surgical parathyroidectomy (7). Despite improved surgical outcomes, this is still a complex procedure in very young patients (2) (8). Few surgeons have parathyroidectomy experience in infants due to the rarity of the disorder. The need for medical management of other PTH-dependent hypercalcemic disorders drove the development of allosteric CASR agonists, namely cinacalcet (9). Three previous case studies have shown the successful use of cinacalcet, in NSHPT (8) (10) (11). Here we report the cases of two unrelated patients with de novo R185Q heterozygous inactivating CASR mutations and highlight their rapid biochemical and clinical response to treatment with cinacalcet.

Case presentation: case 1

Patient 1 was a term male infant with global hypotonia, bell-shaped chest, and metaphyseal irregularities (Fig. 1) that led to an initial clinical diagnosis of Juene’s syndrome. This is an autosomal recessive skeletal ciliopathy causing a short-rib thoracic dysplasia, short-limbed short stature, and severe thoracic constriction (12). The Juene’s syndrome phenotype is variable but to our knowledge does not include hypercalcemia (12). He later presented to endocrine care at age 11 months after additional review of the radiographs indicated diffuse osteopenia, short ribs with irregular rib ends, and metaphyseal sclerosis at the ends of multiple long bones, suggesting a metabolic bone disease, and biochemical evaluation revealed hypercalcemia (Table 1).

Investigation: case 1

Primary hyperparathyroidism was evident with hypercalcemia, consistent with excessive calcium load filtered at the glomerulus. Retrospectively, hypercalcemia (11.7–12.9 mg/dl) had been present on lab testing in the neonatal period, but had not been investigated until seen by endocrinology at 11 months of age. At this age he had gross motor, fine motor and speech delays and dysphagia requiring gastrostomy tube feedings. There was no family history of hypercalcemia or bone disease. Both parents were normocalcemic. Sequencing of the CASR gene revealed a heterozygous R185Q missense mutation.

Initial therapy included 0.9% saline, phosphate supplementation, and a low-calcium formula. He had a transient response to a single dose of pamidronate (0.5 mg/kg i.v.), but serum calcium rose to 13.8 mg/dl after only 2 weeks. Therefore, definitive therapy was sought.

Treatment: case 1

Cinacalcet, 15 mg orally twice daily (3.7 mg/kg per day), was begun at 13 months of age based on dosing from the first published case report (11). The tablets were crushed

Figure 1
(A) Chest X-ray for patient 1, at 1 month of age, shows an elongated and narrowed rib cage with irregular rib ends (arrows). The rib cage was also narrow in an anteroposterior direction (not shown). (B) There are areas of sclerosis in the distal radius and ulna at 1 month of age (arrow).
and dissolved in water for enteral administration. Calcium levels normalized (10.4 mg/dl) within 4 weeks and phosphorus levels rose to near normal (4.3 mg/dl) (Fig. 2A). The low-calcium formula was discontinued and calcium restriction lifted. The cinacalcet dose ranged from 30 to 60 mg/day (2.4–7.4 mg/kg per day) in two to four divided doses to target serum calcium levels below 12 mg/dl (Fig. 2B). Phosphorus supplementation was discontinued at 16 months of age. PTH and alkaline phosphatase levels normalized with only brief elevations and ranged between 30–78 pg/ml and 209–565 U/l respectively.

### Outcome and follow-up: case 1

To date, patient 1 has continued cinacalcet monotherapy for 32 months without adverse incident. Calcium levels have remained slightly elevated (10.4–12 mg/dl) except for one time point when a dose increase was required. PTH levels have been maintained in the normal range. Our patient experienced mild nausea and vomiting after one dose increase, but these well-known side effects of cinacalcet resolved with a dose decrease. His developmental delays improved slowly and at 3 years of age he no longer required interventional services. His dysphagia resolved and his gastrostomy tube was removed 5 months after starting cinacalcet. His weight (3–10th percentile) and height (10–25th percentile) steadily increased while taking cinacalcet. He has not experienced fractures and does not complain of bone pain.

### Case presentation: case 2

Patient 2, a term female infant, presented at 26 days of age with failure of linear growth, poor weight gain, and cough. A chest X-ray was obtained showing multiple rib fractures. Subsequently, a skeletal survey revealed diffusely osteopenic bones with coarse trabecular markings, diffuse symmetric periosteal reactions, and healing lateral right fourth to ninth and left seventh to ninth rib fractures (Fig. 3).

### Investigation: case 2

Laboratory evaluation revealed hyperparathyroidism (Table 1). There was no family history of hypercalcemia or bone disease. Both parents were normocalcemic. Sequencing of the CASR gene revealed a heterozygous R185Q missense mutation. Infusion of fluids with 0.9% saline, oral phosphorus supplementation, and a
low-calcium formula were initiated. Calcium levels decreased to 11–12 mg/dl, but the patient had worsening respiratory distress and was diagnosed with adenovirus. She required ventilator support for 5 days. Notably, calcium levels were controlled during this time (11.4–11.5 mg/dl). Her respiratory distress resolved and after demonstrating adequate weight gain she was discharged on only a low-calcium formula and phosphorus supplementation. She maintained a calcium level generally below 12 mg/dl but significant PTH and alkaline phosphatase elevations developed over the next 12 weeks (Fig. 4A and B).

### Treatment: case 2

Cinacalcet, 6 mg orally daily (2 mg/kg per day), was initiated at 4 months of age. Our hospital’s pharmacy made a compounded solution (6 mg/ml) to allow for small doses. Initial dosing and titration was done in an inpatient environment to monitor for side effects and obtain frequent laboratory monitoring. A decrease in her calcium level from 12.5 to 11.9 mg/dl was noted over 18 h. Cinacalcet dose titrations normalized her PTH in 11 days and her serum calcium remained within our goal of <12 mg/dl during this time (Fig. 4 A, B and C). Alkaline phosphatase decreased gradually and normalized after 15 weeks of cinacalcet therapy. Our patient remained mildly hypercalcemic (10.5–12.7 mg/dl) and dose increases were performed for values above 12 mg/dl while targeting a normal PTH and alkaline phosphatase. She experienced no symptoms from the intermittent hypercalcemia, and the highest calcium values were noted after missing cinacalcet doses. Specific doses ranged between 6 mg daily and 10 mg three times a day orally (1.68–2.7 mg/kg per day) over 13 months of therapy.

### Outcome and follow-up: case 2

She experienced no adverse side effects from cinacalcet, including hypocalcemia. A renal ultrasound at 1 month of age (before therapy) demonstrated mild nephrocalcinosis.
that was stable at 9 months of age. Her rib fractures demonstrated healing by radiograph at 4 months of age and she experienced no further fractures. She had improved weight gain after reduction in her calcium levels (50th percentile for weight and 25th percentile for length at 4 months), which continued after starting cinacalcet (90th percentile for weight and 75th percentile for length at 12 months). Her development throughout her first year of life was normal and without any noted delays.

**Discussion**

We present the successful medical management of symptomatic hypercalcemia due to NSHPT with cinacalcet mono-therapy. Our cases responded similarly to the three reported cases of NSHPT treated successfully with cinacalcet and reinforce that medical management without surgery can successfully control the hypercalcemia and its sequelae in NSHPT due to the dominant negative heterozygous R185Q mutation. The rare nature of NSHPT makes it unlikely that randomized clinical trials will be feasible, highlighting the value of detailed case reports.

To date, there have been three published cases of NSHPT successfully treated with cinacalcet (reviewed in Table 2) (8) (10) (11). The first, in 2011, was an infant with the heterozygous R185Q CASR mutation treated with cinacalcet at 3 weeks of age (11). This patient responded well with long-term normalization of PTH levels and near normalization of calcium levels without reported side effects (11). The second report, in 2012, described a child with a homozygous CASR mutation treated with cinacalcet at 6 years of age with normalization of PTH and near normalization of calcium levels (8). The third case, in 2014, was a newborn with the heterozygous R185Q mutation (10). This patient had a similar course and the authors emphasized that calcium levels may not normalize because of the dominant inhibitor effect of the abnormal CASR protein (10).

Both of our patients also had continued mild hypercalcemia with normalization of PTH and phosphorus levels despite increased cinacalcet doses. We targeted a calcium level below 12 mg/dL for several reasons. Levels in this range are less likely to induce symptoms and patients with FHH have similar levels without adverse long-term effects.

Our first patient had a bell-shaped chest, a feature that has been observed in other case reports of patients with a R185Q CASR mutation (10) (13). He initially received a

---

Table 2: Published cases of neonatal severe hyperparathyroidism treated successfully with cinacalcet.

<table>
<thead>
<tr>
<th>References</th>
<th>Starting dose of cinacalcet</th>
<th>Cinacalcet dosing range</th>
<th>Therapy duration</th>
<th>Therapy initiation</th>
<th>Other therapy used</th>
<th>Mutation</th>
<th>Growth of patient</th>
<th>Other therapy used</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(10)</td>
<td>0.4 mg/kg per day</td>
<td>0.4–9.6 mg/kg per day</td>
<td>18 months</td>
<td>Newborn period</td>
<td>Saline, phosphate, and cholecalciferol</td>
<td>Inherited, heterozygous c.554G→A (R185Q)</td>
<td>12 months</td>
<td>Growth parameters recovered by 5 months of age</td>
<td>Saline, phosphate, and furosemide</td>
</tr>
<tr>
<td>(11)</td>
<td>4 mg daily</td>
<td>40–90 mg daily</td>
<td>22 days</td>
<td>22 days</td>
<td>PAMIDRONATE, phosphate, hydration</td>
<td>De novo heterozygous c.554G→A (R185Q)</td>
<td>6 years</td>
<td>Growth parameters recovered and followed – 1.50 S.D.</td>
<td>Saline, low calcium formula, phosphate, and furosemide</td>
</tr>
<tr>
<td>(8)</td>
<td>30 mg daily</td>
<td>30–60 mg daily</td>
<td>12 months</td>
<td>12 months</td>
<td>Pamidronate, phosphate, hydration</td>
<td>Inherited, homozygous c.206G→A (R69H)</td>
<td>6 years</td>
<td>Growth parameters recovered by 3 months of age and improved thereafter</td>
<td>Saline, low calcium formula, and phosphate</td>
</tr>
<tr>
<td>(13)</td>
<td>4 mg/kg per day</td>
<td>4–30 mg/kg per day</td>
<td>4 months</td>
<td>4 months</td>
<td>Saline, phosphate, and pamidronate</td>
<td>De novo heterozygous c.554G→A (R185Q)</td>
<td>13 months</td>
<td>Growth parameters recovered by 3 months of age and improved thereafter</td>
<td>Saline, low calcium formula, and phosphate</td>
</tr>
</tbody>
</table>

(ID: 15-0040; July 2015 DOI: 10.1530/EDM-15-0040)
diagnosis of Juene’s syndrome, leading to a delay in NSHPT diagnosis. Therefore, NSHPT should be in the differential of a newborn with a bell-shaped chest, osteopenia, and periosteal reactions.

Hypercalcemia can cause many devastating symptoms, including the developmental delays seen in our first patient. Importantly, he had marked improvement once his calcium levels decreased. Our second patient was treated at a young age and hence did not experience developmental delays. Both patients gained weight and height well and experienced no significant adverse side effects directly from cinacalcet therapy.

Cinacalcet was not initiated immediately at diagnosis in patient 2 for several reasons: she had initial clinical and biochemical improvement with low-calcium formula alone; there were reports that hyperparathyroidism in an infant with a heterozygous inactivating CASR mutation born to a normocalcemic mother may improve over time (11) (14); and a clinical trial investigating cinacalcet use for hyperparathyroidism in pediatric patients with chronic kidney disease had just announced a death and been halted (15). However, evidence of worsening skeletal turnover necessitated beginning treatment and after discussion with the parents regarding the risks and benefits of the alternatives, cinacalcet was chosen and consent for treatment signed. Although no long-term pediatric safety analysis is available for cinacalcet, we propose continued monitoring of calcium, phosphorus, PTH, and alkaline phosphatase levels to direct dosing and ongoing intermittent monitoring of kidney function, urinary calcium, and renal ultrasounds. We plan to continue therapy indefinitely, as the alternative requires parathyroid surgery to manage serum calcium. It may, however, be possible to taper off treatment while monitoring serum calcium, as our first patient has had a steady decrease in his dose as he has grown (Fig. 2B).

Despite the above reported successes, in vitro studies have shown varying effects of cinacalcet in different CASR mutations, suggesting that cinacalcet may not be effective in every case. The residual functionality of the CASR protein and location of the mutation in the transmembrane receptor may be important predictors of success with cinacalcet treatment (16). In accordance, two cases of NSHPT have been described where cinacalcet therapy failed (13) (17). These cases had different CASR mutations from each other, but both resulted in a nonfunctional protein due to truncating mutations. A cataloguing of CASR mutations and their response to therapy may be a valuable asset in determining treatment for NSHPT.

In conclusion, we report two cases of NSHPT caused by a heterozygous inactivating dominant negative CASR mutation that responded very well to cinacalcet monotherapy. Our patients also showed improvements in bone structure and did not fracture while on cinacalcet therapy. While the response to cinacalcet will be dictated by residual function of the CASR protein, we suggest that a trial of cinacalcet be undertaken in infants and children with significant hypercalcemia and metabolic bone disease secondary to CASR mutations.


Received in final form 18 May 2015
Accepted 18 June 2015