TREATMENT EXPERIENCE AND LONG-TERM FOLLOW-UP DATA IN TWO SEVERE NEONATAL HYPERPARATHYROIDISM CASES

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INTRODUCTION

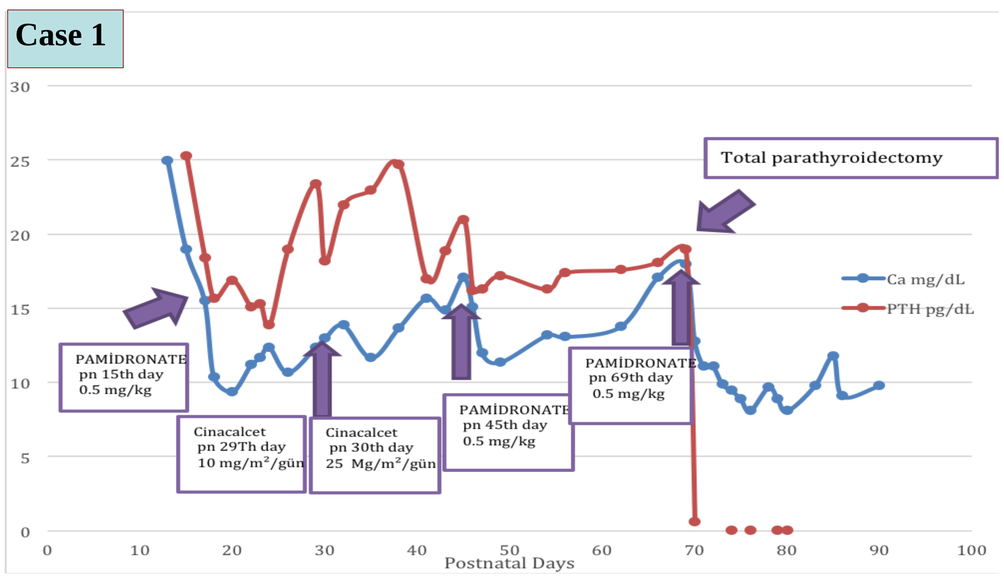
Familial benign hypocalciuric hypercalcemia (FBHH) and neonatal severe hyperparathyroidism (NSHPT) are associated with loss of CASR function. Homozygous or compound heterozygous mutations typically cause NSHPT, an autosomal-recessive disorder associated with life-threatening hypercalcemia and multiple fractures. We here report two cases with NSHPT together with their treatment and long-term follow-up.

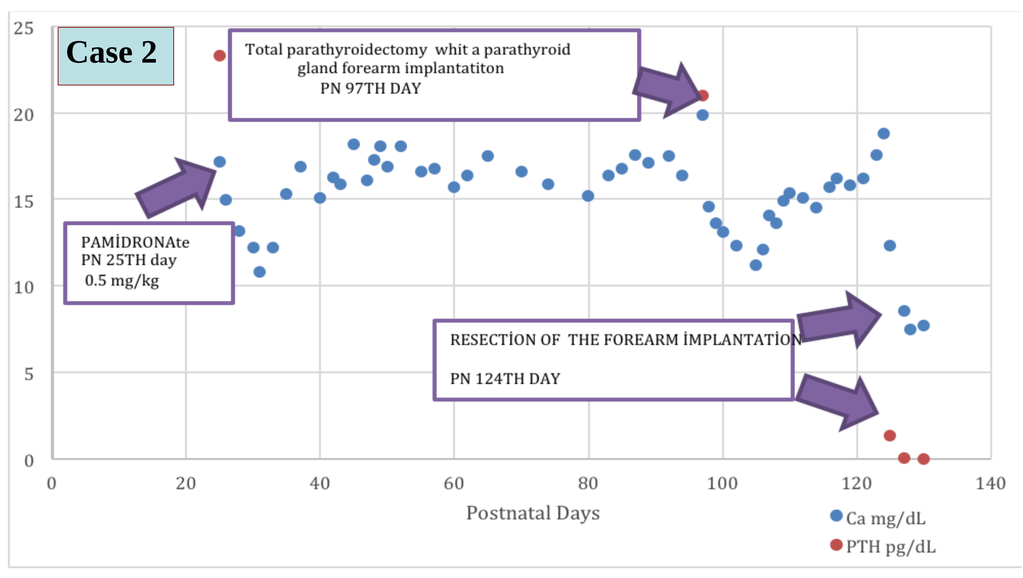
CASE REPORT

CASE 1: A 12-day-old was referred to our hospital with hypercalcemia (Ca: 25 mg/dL; normal range [NR]: 8.8–10.8 mg/dL). On physical examination, he was conscious but restless. Ca, 19.4 mg/dL (NR 9–10.8 mg/dL); phosphate (P), 3.3 mg/ dL (NR 4.5–6.7 mg/dL); alkaline phosphatase (ALP), 412 IU/L (NR 110–302 IU/L); PTH, 2,536 pg/mL (NR 11–67 pg/mL); urine Ca, 25.5 mg/dL; urine creatinine (Cr), <0.5 mg/dL; urine Ca/Cr, 51; 25-hydroxy vitamin D, 18.6 µg/dL (NR 10–80 µg/dL); and 1,25-dihydroxy vitamin D, 21.3 pg/mL (NR 16–65 pg/mL). A parathyroid technetium-99M sestamibi radionuclide scan was normal without evidence of parathyroid adenoma.

CASE 1: This patient with severe hypercalcemia was started on intravenous hyperhydration, furosemide (1 mg/kg every 4 h), and prednisone (1 mg/kg every 6 h). This treatment did not cause a significant decrease in serum levels of Ca and pamidronate was administered at a dose of 0.5 mg/kg intravenously on the 15th postnatal day. Ca level increased on the 20th postnatal day, and cinecalcet treatment was started at a dose of 10 mg/m^2/day on the 29th postnatal day. Hypercalcemia and hyperparathyroidism did not decrease; thus, the cinecalcet dose was increased to 25 mg/m^2/day on the 30th postnatal day. But hypercalcemia did not decreased. Total parathyroidectomy was performed on the 70th postnatal day and the serum levels of PTH were 67 pg/mL following the surgery (Figure 1). Histopathological examination of the parathyroid glands revealed chief cell hyperplasia. Sequence analysis revealed a previously undefined homozygous c.1630C>T in the patient's *CASR* gene, which was heterozygous in both parents, resulting in a truncation at the extracellular N-terminal domain of the protein.

CASE 2: A 25-day-old female neonate born at term presented with severe hypotonia, listlessness, feeding difficulties, and failure to thrive. Ca, 17.2 mg/dL (NR 8.8–10.8 mg/dL); P, 2.8 mg/dL (NR 4.5–6.7 mg/dL); ALP, 314 IU/L (NR 110–302 IU/L); PTH, 2330 pg/mL (NR 11–67pg/mL); 25-hydroxy vitamin D, 15.6 µg/dL (NR 10–80 µg/dL); and Ca/Cr clearance ratio, 0.0004. Total parathyroidectomy and forearm implantation of a parathyroid gland were performed at 97 days of age. The patient was not able to make eye contact or hold her head upright for short periods of time during the neurological examination before parathyroidectomy, and there was mild developmental retardation. Serum levels of Ca decreased gradually until the 105th postnatal day, but subsequently increased again (Ca, 18.8 mg/d; PTH, 133 pg/mL). The patient's implanted parathyroid gland was removed at 124 days of age. A genetic analysis was revealed a point mutation (*c.2045C>T; p.Pro682Leu*) in the *CASR* gene that was homozygous in the patient and heterozygous in the parents.





Case 1 is now 1.5 years old, and his height and weight are 81 cm (25–50th percentile) and 10.7 kg (10–25th percentile). Neuromotor development is consistent with his age.

Case 2 is now 15 years old, and her height and weight are 165.9 cm (1.2 SDS) and 64.6 kg (1.21 SDS), respectively. The patient's neuromotor development is normal and her IQ score of 60 is consistent with mild mental retardation. Normocalcemia was ensured with calcitriol treatment, and a bone mineral density evaluation revealed an L1-2 value of 1.514 gr/cm^2 and a Z-score of +3. No bone deformities or fractures developed during follow-up.

DISCUSSION

The medical management of NSHP cases is often difficult and complex. A prompt assessment of the type of mutation that affects the CASR protein is desirable to determine whether a calcimimetic treatment is suitable.

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