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Case Report

Novel homozygous inactivating mutation of the calcium-sensing receptor gene (*CASR*) in neonatal severe hyperparathyroidism—lack of effect of cinacalcet

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ABSTRACT

Background: NSHPT is a life-threatening disorder caused by homozygous inactivating calcium-sensing receptor (*CASR*) mutations. In some cases, the CaSR allosteric activator, cinacalcet, may reduce serum PTH and calcium levels, but surgery is the treatment of choice.
Objective: To describe a case of NSHPT unresponsive to cinacalcet.
Patient and Results: A 23-day-old girl was admitted with hypercalcemia, hypotonia, bell-shaped chest and respiratory distress. The parents were first-degree cousins once removed. Serum Ca was 4.75 mmol/l (N: 2.10–2.62), P: 0.83 mmol/l (1.55–2.64), PTH: 1096 pg/ml (9–52) and urinary Ca/Cr ratio: 0.5 mg/mg. First, calcitonin was given (10 IU/kg × 4/day), and then 2 days later, pamidronate (0.5 mg/kg) for 2 days. Doses of cinacalcet were given daily from day 28 of life starting at 30 mg/m^2 and increasing to 90 mg/m^2 on day 43. On day 33, 6 days after pamidronate, serum Ca levels had fallen to 2.5 mmol/l but, thereafter, rose to 5 mmol/l despite the cinacalcet. Total parathyroidectomy was performed at day 45. Hungry bone disease after surgery required daily Ca replacement and calcitriol for 18 days. At 3 months, the girl was mildly hypercalcemic, with no supplementation, and at 6 months, she developed hypocalcemia and has since been maintained on Ca and calcitriol. By *CASR* mutation analysis, the infant was homozygous and both parents heterozygous for a deletion–frameshift mutation.
Conclusion: The predicted nonfunctional CaSR is consistent with lack of response to cinacalcet, but total parathyroidectomy was successful. An empiric trial of the drug and/or prompt mutation testing should help minimize the period of unnecessary pharmacotherapy.

Introduction

Neonatal severe hyperparathyroidism (NSHPT) is a rare clinical entity caused by homozygous inactivating mutations in the calcium-sensing receptor (*CASR*) gene [1–4]. NSHPT results in severe hypercalcemia, metabolic bone disease and potential neurodevelopmental deficits, all of which may be life-threatening [5]. The CaSR protein is a G-protein-coupled receptor expressed most abundantly in parathyroid chief and renal tubular cells [2]. The activity of the parathyroid CaSR regulates parathyroid hormone (PTH) secretion and PTH synthesis and parathyroid cell proliferation [2]. The relationship between extracellular ionized calcium and PTH concentrations is best modeled as an inverse sigmoidal curve [2]. The activity of the CaSR determines the calcium set point—that is, the extracellular calcium concentration at which PTH secretion is half-maximally inhibited. [2]. While individuals with familial hypocalciuric hypercalcemia (FHH) due to heterozygous inactivating *CASR* mutations usually exhibit a modest rightward shift in the Ca-PTH response curve, in NSHPT with homozygous *CASR* inactivation, there is a dramatic rightward shift and a greatly elevated calcium set point [6,7].

Hypercalcemia in such cases is usually severe, and immediate medical and/or surgical treatment may be needed if a favorable outcome is to be assured [8]. Therapeutic options for NSHPT infants with symptomatic hypercalcemia and hyperparathyroidism include intravenous fluid hydration and loop diuretic therapy (albeit with careful monitoring of volume status), calcitonin and, more recently, bisphosphonates and calcimimetics

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[9–13]. However, medical management of such cases is often difficult and complex.

Herein, we present a case of NSHPT caused by homozygous mutation in the *CASR* gene and review the challenging clinical course that reveals the difficulties in management of this condition. The study suggests the benefits of an empiric trial of a calcimimetic as monotherapy and early mutation identification.

Patient, methods and results

Case report

Protocols were approved by Institutional Ethics Committees. The parents of the proband provided informed consent. The proband (individual V-1; Fig. 1) is a 3240-g (50th percentile) female infant born by spontaneous vaginal delivery at term. The parents are first-degree cousins once removed (Fig. 1). The neonate required ventilatory support for respiratory distress on day 2 of life. Unresolving pneumonia and hypercalcemia (day 21) prompted referral to Marmara University Hospital Neonatal Intensive Care Unit (NICU) on day 23. At presentation, weight was 3200 g (10th percentile), length 54 cm (50th percentile) and head circumference 35 cm (50th percentile). Blood pressure and heart rate were normal. She had generalized hypotonia, coarse facial features, a bell-shaped chest and signs of respiratory distress. Biochemistries were as follows: serum calcium, 4.75 mmol/l (normal: 2.10–2.62); phosphate, 0.83 mmol/l (1.55–2.64); PTH, 1096 pg/ml (9–52); alkaline phosphatase (ALP), 577 IU/L (neonate: 145–420); 25-hydroxyvitamin D, 88 nmol/L (>75); and urinary calcium/creatinine ratio, 0.5 mg/mg (<0.8). X-rays showed evidence of parathyroid bone disease (Fig. 2). Overall, the skeleton was undermineralized, but the architecture was not greatly distorted. Cyst-like structures at distal ends of both humeri were noted along with destruction of distal clavicles, distorted barely visible scapulae and bell-shaped rib cage with patchy lytic destruction of upper ribs. There was severe generalized bone demineralization and osteopenia with coarse trabeculation and subperiosteal resorption.

Biochemical profiles for the father (III-9) were consistent with FHH with serum calcium, 2.8 mmol/l; phosphate, 0.8 mmol/l (0.87–1.45); PTH, 36 pg/ml; ALP, 64 IU/L (adult: 50–270); and urinary calcium/creatinine ratio (mg/mg), 0.08. The mother (IV-1) had serum calcium, 2.42 mmol/l; phosphate, 1.09 mmol/l; PTH, 52 pg/ml; and urinary Ca/creatinine ratio (mg/mg), 0.01.

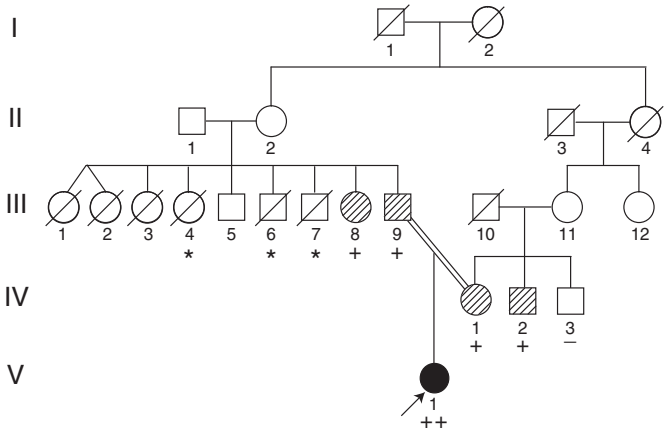

Fig. 1. Pedigree of family with FHH/NSHPT. Clinical status is indicated by open symbols (unaffected or status not known), hatched symbols (FHH) and solid symbols (NSHPT). The proband is indicated by the arrow. Family history revealed that several of the father's siblings had died at an early age or suffered mental retardation and cortical blindness. (*) Blindness and mental retardation; (+) presence; (−) absence of a mutated *CASR* allele. III-1, III-2, died at 1 week of age; III-3, died at age of 6 months; III-4, died at age of 26 years; III-6, died at age of 17 years; III-7, died at age of 3 years.

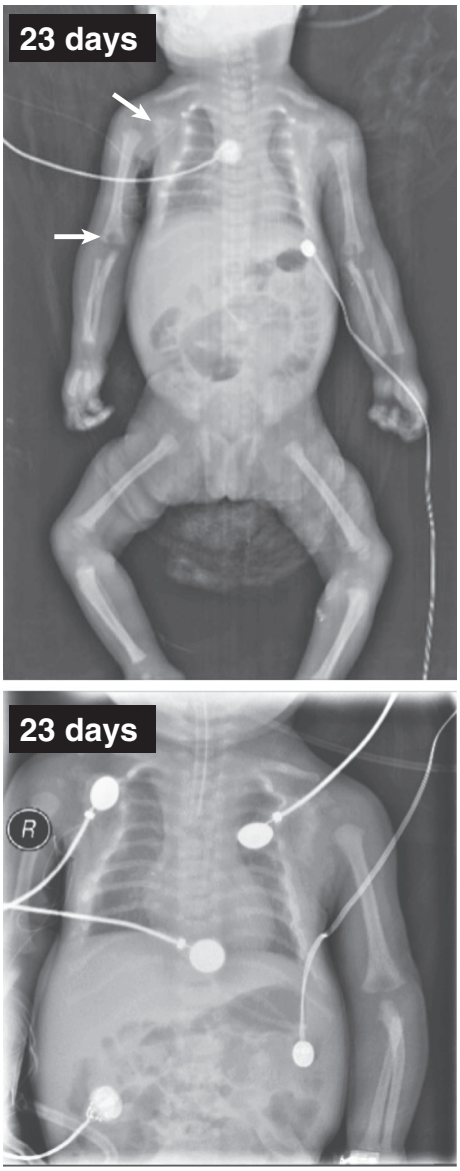

Fig. 2. Radiographs of proband V-1 at 23 days of age. No long bone fractures had occurred. Defects of clavicle, scapula (arrow), rib, humerus (arrow), radius, ulna and femur and generalized undermineralization can be noted.

Treatment

In the NICU, the infant was treated with iv fluids and furosemide. The hypercalcemia did not improve, and on day of life (DOL) 25, calcitonin was given subcutaneously (10 U/kg) at 6 h intervals for 48 h without beneficial effect (Fig. 3A). Pamidronate (0.5 mg/kg/day iv) was given on DOL 27 and 28. While there was no apparent immediate decrease in the serum calcium, PTH increased to 1600 pg/l. Therefore, cinacalcet (30 mg/m^2/day) was started on DOL 28. Serum calcium levels decreased to 2.5 mmol/l on DOL 33, the 5th day of cinacalcet treatment, at which time the dose was decreased to 15 mg/m^2/day. The calcium levels remained normal for 2 days but thereafter returned over the course of several days to 5 mmol/l. Increasing the dose of cinacalcet—30 mg/m^2/day (DOL 36–38), 60 mg/m^2/day (DOL 39–42) and 90 mg/m^2/day (DOL 43 and 44)—was ineffective in counteracting the rising hypercalcemia (Fig. 3A). Finally, total parathyroidectomy (PTX) without autotransplantation was performed on DOL 45. All four of the excised parathyroid glands were hyperplastic, measuring about 8 mm (normal, 3–6) in length. Serum calcium levels fell to within the