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Case Report

Is calcium signaling relevant for long bone growth?

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ABSTRACT

Background: Neonatal severe hyperparathyroidism (NSHPT) is a rare autosomal recessive disorder of calcium homeostasis, more often induced by homozygous inactivating mutations of the calcium-sensing receptor gene. This rare syndrome can be lethal if total parathyroidectomy is not performed within the first weeks of life.
Clinical report: We report the clinical case of a male patient, son of consanguineous hypercalcemic parents, with clinical and biochemical features of NSHPT, followed until the age of 21 years. The patient underwent total parathyroidectomy, and then, due to the low compliance to calcium and calcitriol supplementation, an attempt was made with recombinant human parathyroid hormone [rhPTH (1–84)]. The patient did not reach the predicted height with an increased ratio of the upper and lower segments.
Conclusions: While this case is unique for the length of follow-up, the continuous and detailed description of NSHPT after total parathyroidectomy in its adult phenotype, and the treatment of hypoparathyroidism with rhPTH (1–84). Following this first description of a statural defect due to shortening of long bones in NSHPT, future investigations will attempt to uncover the role of calcium signaling in growth plate cartilage in humans.

Introduction

Neonatal severe hypoparathyroidism (NSHPT; OMIM 2439200) is a rare autosomal recessive disorder of calcium homeostasis. NSHPT manifests itself in the first 6 months of life, but is often discovered in the first few weeks postnatally [1–3]. Classical NSHPT is caused by homozygous inactivating mutations of the calcium sensing receptor (*CaSR*) gene [4], with only few cases described so far who were heterozygous for a *de novo* mutation, all of them with a milder disease phenotype than in classical NSPHT [3,5,6]. About 84 cases of NSHPT have been described since 1964 to the present [1,5–23]. Other NSHPT adults successfully treated into adulthood have been reported [14,15], mostly lacking an uninterrupted clinical, radiologic, and laboratory follow-up.

Classically, NSHPT is characterized by parathyroid hyperplasia, marked and symptomatic PTH-dependent hypercalcemia, relative hypocalciuria [14], and bone fragility [1–3]. Early radiologic findings in this disease include bony demineralization, pathologic fractures of long bones and ribs (in 55% of cases), subperiosteal resorption (in 45% of cases), rib fractures and rachitic changes (in 30% of cases) [18,24]. Infants with NSHPT often exhibit polyuria, dehydration and hypotonia associated with a history of failure to thrive, respiratory distress, irritability, lethargy, constipation, and delayed neuropsychological development [2,14,25,26]. All these disturbances are more evident if HPT is not promptly cured.

NSHPT can be fatal if partial or total parathyroidectomy, the standard treatment for most patients, is not carried out within the first several weeks of life, with a good short-term prognosis after surgery and rapid involution of bony abnormalities [26,27]. The use of autotransplantation of the parathyroid tissue showed a modest beneficial effect, with potential recurrence of primary HPT later in life [11]. Only in one case of neonatal HPT caused by a heterozygous inactivating mutation of the *CaSR* gene the treatment was exclusively pharmacological with calcimimetics (Cinacalcet) [19,28]. The explanation for this apparently paradoxical response is that there are inactivating *CaSR* gene mutations in which a calcimimetic increases responsiveness to extracellular calcium [29–31]. Intravenous aminobisphosphonates are used in NSHPT to control severe hypercalcemia prior parathyroidectomy or as a rescue therapy to stabilise life-threatening demineralization [16,17,19].

We report the clinical case of a 21-year-old, the son of consanguineous parents affected by Familial Hypocalciuric Hypercalcemia (FHH; OMIM 145980), who had manifested the clinical and biochemical features of NSHPT. The surgical and medical treatments of this patient and his 21 year clinical course are described. This case is unique for the 21 years continuous and detailed description of follow-up of NSHPT, for the use of recombinant human parathyroid hormone 1–84 [rhPTH (1–84)] as a substitutive therapy for the post-surgical refractory hypoparathyroidism, and for the relevant skeletal abnormalities described.

Abbreviations: PTH, Parathyroid hormone; CaSR, Calcium-sensing receptor; NSHPT, Neonatal severe hyperparathyroidism.

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Clinical report

The patient, a boy, was born in 1990 after a gestation of 40 weeks by cesarean delivery due to breech presentation. The parents were first cousins, without a history of kidney stones or other disorders of bone or mineral metabolism. His birth weight was 3000 g, with a head circumference of 39.5 cm, and a birth length of 50 cm. During delivery the patient suffered a spontaneous diaphyseal fracture of his left femur. The child also had intrauterine rib fractures, respiratory distress syndrome, inability to suck, and hypotonia.

At birth, laboratory evaluation showed the following values: total serum calcium 6.85 mmol/L (n.v. 2.05–2.55), ionized serum calcium 3.5 mmol/L (n.v. 1.15–1.27), serum phosphorus 1,29 mmol/L (n.v. 0.74–1.52), serum magnesium 0.76 mmol/L (n.v. 0.65–1.05), alkaline phosphatase 875 U/L (n.v. 240–840), parathyroid hormone (PTH) 1460 ng/L (n.v. 10–65), 25-hydroxyvitamin D_3 17.47 nmol/L (n.v. 35–150), urinary calcium 2.8 mmol/kg/day (n.v. ≤0,1), creatinine 0.46 mg/dl (n.v. 0.5–4.1), creatinine clearance 13 mL/min (n.v. 13–58), and urine calcium/creatinine index 9.6 mg/mg (n.v. in neonates < 0.8 mg/mg).

Clinical course and management

Neonatal period

Biochemical exams, surgery treatment, and histological examination. Blood tests confirmed the diagnosis of primary HPT, with negative parathyroid ultrasound. The diagnosis of NSHPT was suspected based on the early onset of PTH-dependent hypercalcemia, its severity, and the consanguinity of the hypercalcemic parents [20]. The hypercalciuria, observed at birth, could be explained by extremely high levels of serum calcium, with calcium filtered exceeding the renal resorptive capacity. In the first 30 days the patient was treated with furosemide carbocalcitonina 6/U/kg/day and 1.5 mg/kg/day, the ionized calcium were only partially controlled (varied between 3.11 and 3.32 mmol/L, n.v. 1.15–1.27). At the age of 30 days the patient underwent total parathyroidectomy. Histological examination confirmed hyperplasia of all parathyroid glands. Preoperative ionized calcium was 2.08 mmol/L (n.v. 1.15–1.27), with a drop to 1.46 mmol/L at the end of surgery and a significant decrease of total serum calcium to 2 mmol/L during the immediate postoperative time, with a consequent need for calcium and oral calcitriol administration.

Imaging studies. At 2 months of age, ultrasound showed slightly enlarged kidneys, with diffuse parenchymal hyperechogenicity and complete disappearance of the cortico-medullary junction, referred to as calcium deposits typical of nephrocalcinosis. This kidney complication was evident up to 11 months of age and then it disappeared with reappearance of the cortico-medullary junction

At 2 months of age, a transfontanellar ultrasound did not show pathological changes, with lack of cerebral calcifications. The eye examination did not show any abnormalities.

At 4 months of age radiological skeletal abnormalities encompassed: the slightly oval appearance of the iliac wings, the horizontalization of the acetabular roof, the delayed maturation of the growth plate, the demineralization and bowing of tibia and fibula (Fig. 1A). These findings can be related to primary HPT [3,8,26,32,33].

Genetic analysis. Informed consent for genetic testing was obtained from the parents. Sequencing of the *CaSR* gene [34] revealed a homozygous missense mutation at codon 66 exon 3 (CGT-TGT) of the gene [20]. The mutation detected (p.R66C) was predicted to change a restriction site and was confirmed by digestion with relevant restriction enzymes. Mutational analysis of the *CaSR* gene confirmed the diagnosis of FHH in all the hypercalcemic subjects of the family including the parents, the maternal grandfather, a maternal aunt, and the paternal grandmother (Fig. 2, Table 1) [20]. Moreover, prenatal genetic analysis of a younger brother showed the presence of the *CaSR* gene mutation in the heterozygous state.

Childhood and puberty

Biochemical exams

The profile of yearly average serum calcium and urinary calcium 24/h from 1 to 19 years of age is shown in Fig. 3A–B. Despite supplementation with oral calcium and calcitriol, wide variations of serum calcium levels, corrected for serum albumin, were evident from 1.85 mmol/L to 2.92 mmol/L (n.v. 2.05–2.55), with undetectable PTH. Urinary calcium, corrected for creatinine, was variable, mostly below normal values, from 80 mg/24 h to 176 mg/24 h (n.v. 100–300), rarely above normal, the maximum value was 310 mg/24 h. The levels of serum and urinary magnesium were always normal. The renal function was normal during childhood and puberty.

In order to evaluate if the homozygous mutation of the *CaSR* gene could influence the endocrine system, at 17 years of age, an extensive hormonal profile was performed. The tested values showed: TSH 0.67 mU/L (n.v. 0.4–4.2), fT4 18.4 pmol/L (n.v. 12–30), fT3 6.56 pmol/L (n.v. 2–7), FSH 2.18 IU/L (n.v. 1.7–11), LH 6.50 IU/L (n.v. 0.6–7.0), testosterone 37.0 nmol/L (n.v. 10.4–41.16), cortisol 201 nmol/L (n.v. 140–690), ACTH 6,55 pmol/l (n.v. 9–52), GH 1.16 μg/L (n.v. 0–18).

Imaging studies

At 14 months of age radiological exam of the pelvis and lower limbs, showed normalization of the morphology of the pelvic bones, normal hip joints, a left femur slightly bowed due to the previous fracture, and bilateral curvature of normally mineralized tibiae and fibulae. These findings were confirmed at 4 and 6 years of age. X-ray examination of the spine and pelvis, executed at 14 years of age, showed mild scoliosis of the lumbar spine with a small intraspongiosae hernia between L3 and L4 and persistence of the bilateral curvature of the tibiae and fibulae. The gait and stance of our patient were normal, and he had no limitations to normal physical activities. The patient did not have skeletal rachitic changes such as rachitic rosary or metaphyseal flaring.

At 5 years of age neck ultrasound showed normal morphology and size of the thyroid. Abdominal ultrasound carried out at 4, 6 and 8 years of age showed lack of kidney calcifications and normal liver, gallbladder, pancreas, and spleen.

Bone densitometry

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA) at 12, 14 and 17 years of age, the values of *Z*-score at the femoral neck were consistently within the normal range (*Z*-score ≥ −2), instead, the *Z*-score at the lumbar spine and forearm (radius and ulna) increased from *Z*-score compatible with low bone mass (*Z*-score ≤ −2.0) to *Z*-score within the range of normal. The femoral neck *Z*-score at 12, 14 and 17 years of age was respectively: 0.7, −0.2 and 1.1. The lumbar *Z*-score (L1–L4), performed at 12, 14 and 17 years of age, was respectively: −2.8, −0.8, and 0.5. The forearm (radius and ulna) *Z*-score, at 14 and 17 years of age, was respectively: 1/3 distal −2.9, mid-distal −2.9, ultradistal −0.9, total −2.5, and 1/3 distal −1.3, mid-distal −0.9, ultradistal −0.4, total −1.0.

Mental and physical development. The growth curve for height followed the 50th percentile up to 14 years of age, with mean target height being 178.5 ± 6 cm. The sexual maturation was normal. The patient led a normal social life, but the performance at school was not optimal, complaining an irritable mood with poor concentration.

Compliance to therapy

With the years the patient never showed a good compliance with medical therapies, as complained by the parents and so referred by the patient. The unsatisfactory adherence to calcium/calcitriol therapy was related to gastroenteric problems.