Recombinant Parathyroid Hormone Therapy for Severe Neonatal Hypoparathyroidism

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Hypoparathyroidism-retardation-dysmorphism (HRD) syndrome (OMIM 241410), also known as Sanjad-Sakati syndrome, is a rare autosomal recessive disorder characterized by hypoparathyroidism, growth failure, developmental delay, and characteristic facies. We describe the effective short-term use (tapered over 12 days) of recombinant parathyroid hormone (PTH) (teriparatide) in an unusual genetic condition characterized by hypoparathyroidism.

Standard treatment for hypoparathyroidism involves oral vitamin D analogues and calcium, often in large doses to achieve sufficient intestinal calcium transport to overcome the hypercalciuria and concomitant malabsorption.[1] Despite its known physiological benefits,[2] recombinant PTH is not usually considered in the treatment algorithm for hypoparathyroidism in the pediatric population.

Case Report

Approval for this case report was obtained from the Human Research Ethics Committee of The Children's Hospital at Westmead. Informed consent was obtained from the family. A female infant was born to first-cousin Iraqi parents at 31 weeks gestation, after an antenatal course that included oligohydramnios and fetal growth restriction. The parents had previously experienced 2 first-trimester miscarriages and fetal death at 30 weeks, and the current pregnancy was conceived after in vitro fertilization. She had a birth weight of 1190 g (SDS, −1.02), length of 36.5 cm (SDS, −1.77), and head circumference of 25.4 cm (SDS, −1.61). Dysmorphic features included deep-set eyes, large ears with hypoplastic posterior helices, and a thin nose (**Figure 1**). The newborn period was complicated by respiratory distress syndrome, treated with surfactant, mechanical ventilation, and continuous positive airway pressure. Significant feeding intolerance and vomiting were present from the first week of life. Upper gastrointestinal studies showed gastric hypomotility and delayed passage into the duodenum with no mechanical obstruction. Transpyloric tube feeding was started at 4 weeks after birth. Fat malabsorption was confirmed by fecal fat analysis and low serum vitamin A and E levels. Results of a sweat test were normal. Pancreatic enzyme replacement and fat-soluble vitamin supplementation was instituted.

Hypocalcemia (corrected plasma calcium, 6.7 mg/dL; normal range, 8.4-10.6 mg/dL) was first detected on day 3. Empirical treatment with calcium and cholecalciferol was started for presumed vitamin D deficiency, given that the mother was veiled and had documented vitamin D deficiency. Subsequently, an inappropriately low PTH level was found on multiple occasions (<2.8 pg/mL; normal range, 9.5-66.5 mg/dL). The infant had a high urine calcium:creatinine ratio (1.5 mM/mM) despite hypocalcemia, an elevated plasma phosphate level (11.7 mg/dL; normal range, 3.7-6.5 mg/dL), and a normal 25-hydroxy vitamin D level (36 ng/mL; normal, >19 ng/mL). Ultrasound did not reveal nephrocalcinosis. Normal parental calcium and PTH levels excluded maternal hyperparathyroidism and inherited calcium-sensing receptor defects. Fluorescence in situ hybridization for 22q11 deletion was negative. X-rays in the neonatal period did not show skeletal abnormalities.

HRD syndrome was suspected on the basis of persistent hypoparathyroidism, prenatal and postnatal growth restriction, and dysmorphic facial features. Analysis of the tubulin-specific chaperone E (TBCE) gene (*TBCE*) confirmed the presence of homozygous 12-bp deletions in exon 2 (c.155-166del12; p.del52-55). Analysis of parental DNA confirmed that both parents were heterozygous for the same mutation.

Recurrent episodes of severe hypocalcemia (nadir total corrected calcium, 3.8 mg/dL) and poor postnatal growth continued. Calcitriol therapy was introduced, and doses were rapidly escalated to 800 ng/kg/day (usual maximum 90 ng/kg/day), delivered via both oral and transpyloric routes to maximize absorption. Magnesium supplementation was started for hypomagnesemia (1.1 mg/dL; range, 1.6-2.4 mg/dL). At 2 weeks corrected gestational age, hypocalcemia refractory to high-dose calcitriol prompted a trial of recombinant PTH (PTH 1-34; teriparatide). A starting dose of 1 μg/kg delivered subcutaneously, followed by twice-daily dosing, minimized fluctuations in ionized calcium levels (**Figure 2**). Levels achieved the normal range

HRD	Hypoparathyroidism-retardation-dysmorphism
PTH	Parathyroid hormone
TBCE	Tubulin-specific chaperone E

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The authors declare no conflicts of interest.

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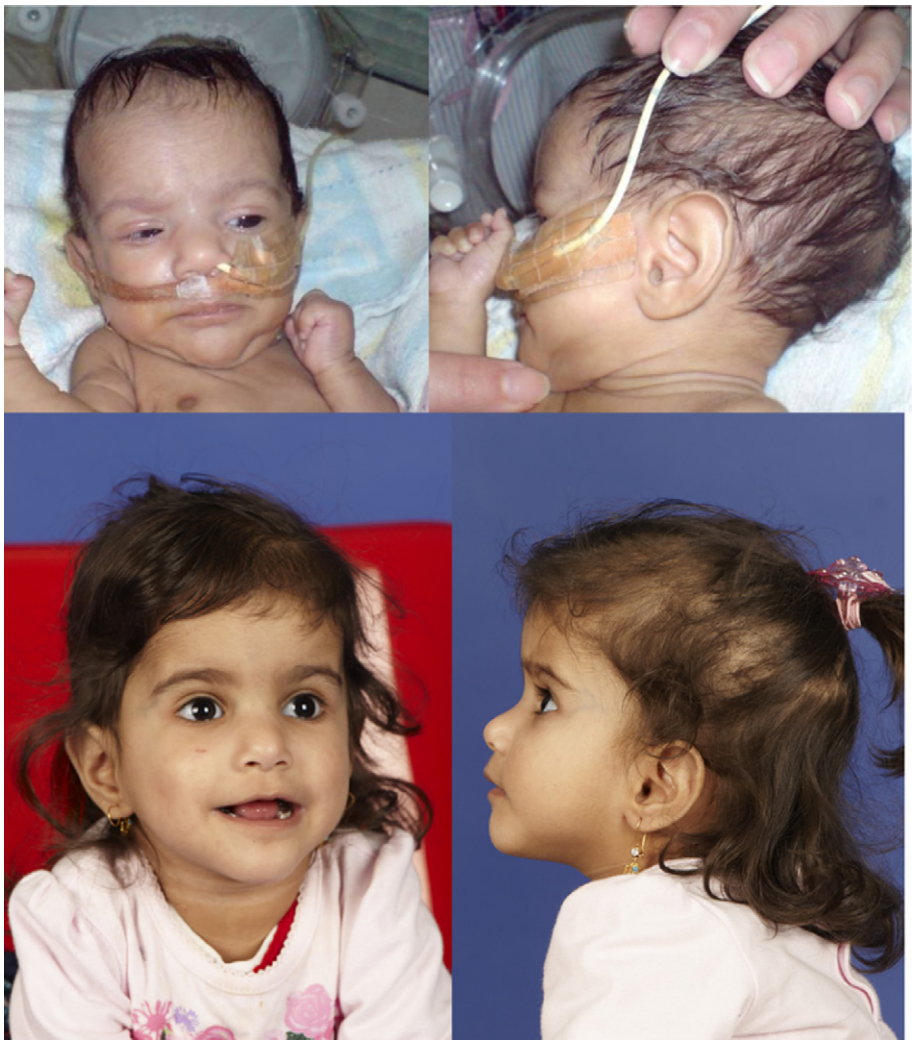

Figure 1. Patient at corrected gestational age 1 week and at age 2.6 years. Dysmorphic features include a high forehead, triangular chin, large low-set ears, a thin upper lip, and deep-set eyes.

by day 6 of therapy, with concomitant improvement of hyperphosphatemia. Teriparatide was weaned and discontinued after 12 days of therapy. Weight gain and alertness also increased, and vomiting improved sufficiently to allow continuation of high-dose oral calcitriol and calcium.

The infant was discharged to home at corrected gestational age 3 months on calcitriol 130 ng/kg/day and magnesium 50 mg/kg/day. By 12 months, calcitriol dose was weaned to 55 ng/kg/day and magnesium supplementation was discontinued. The infant demonstrated significant developmental delay and growth retardation; with length 54.8 cm (SDS, −6.21) and weight 3.69 kg (SDS, −9.73). She had 9 hospital admissions for hypocalcemia or vomiting during her first year of life, not associated with recurrent infections. Pancreatic enzyme supplementation was discontinued after the first year of life, with resolution of steatorrhoea.

Discussion

HRD syndrome is a rare genetic disorder, with the majority of reported patients being of Middle Eastern Arabic origin. The first published case series described 5 infants with hypoparathyroidism and associated hypocalcemic tetany, severe growth restriction, characteristic facial features, and mental retardation.[3] A review of 22 patients reported a mean age of death of 4 years in males and 6.4 years in females, due primarily to sepsis, and a total of 205 hospitalizations in these patients.[4]

Mutations in *TBCE* at chromosome 1q42-43 were first identified in affected patients in 2002.[5] *TBCE* encodes TBCE, one of several chaperones in proteins necessary for α-tubulin folding and α/β-tubulin heterodimer formation. Tubulin folding is essential for construction of microtubules, which as central elements of the cytoskeleton play

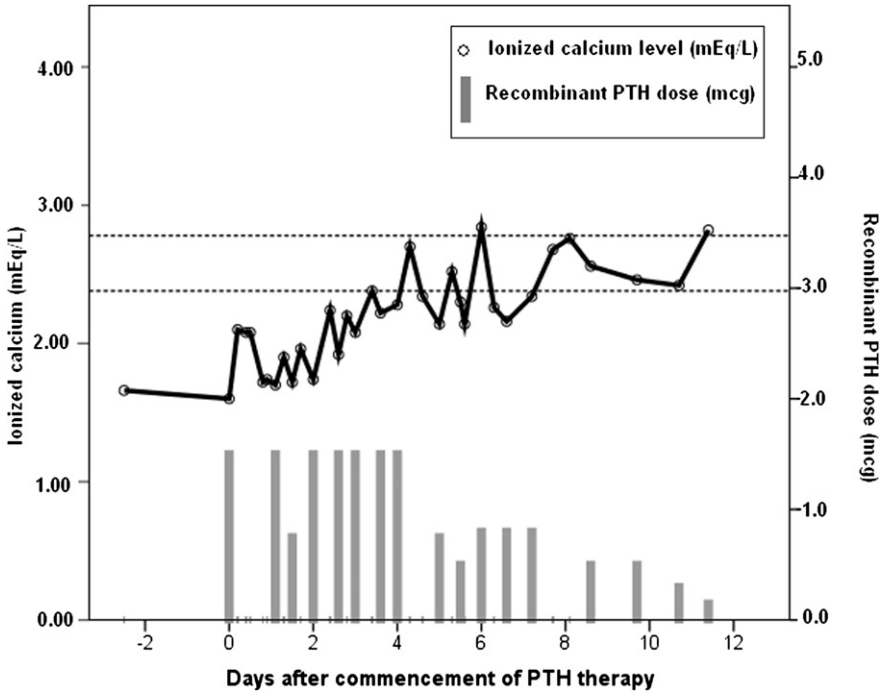

Figure 2. Ionized calcium levels during recombinant PTH therapy.

various roles in multiple cellular processes. In keeping with this central role for tubulin microtubules, a complete absence of TBCE is not viable in model organisms.[6] Autosomal recessive Kenny-Caffey syndrome (OMIM244460), also caused by mutations at the same gene locus, differs by the presence of an extended bone phenotype with osteosclerosis.[5]

The basis of hypoparathyroidism in HRD syndrome appears to be agenesis or dysgenesis of the parathyroid glands.[7] Hypocalcemia often presents in the neonatal period and can be managed with calcium and calcitriol supplementation. In later childhood, patients may remain on calcium supplementation alone. Three patients in the original case reports required aluminium hydroxide gel as a phosphate binder. The use of teriparatide in the pediatric population remains experimental, due primarily to the reported risk of osteosarcoma in rats given supraphysiological doses (50-150 μg/kg/day),[8] with only 1 other case in the literature reporting the use of teriparatide in hypoparathyroidism in infancy.[9] Once-daily teriparatide is used as second-line therapy in adults with osteoporosis, due to its anabolic action on bone.[10] PTH affects calcium homeostasis primarily through its renal action on calcium reabsorption. Preliminary studies have reported the efficacy of twice-daily teriparatide in children with hypoparathyroidism.[2]

In the present case, we judged that the severity of hypocalcemia refractory to conventional therapy, in the context of an infant whose prognosis was guarded, warranted the acute use of teriparatide. PTH, available only in subcutaneous form, provided an effective alternative to conventional oral therapies for hypoparathyroidism and produced predictable effects on calcium homeostasis in our patient during a period of severe feeding intolerance and malabsorption. Malabsorption improved, allowing maintenance therapy with oral calcitriol and calcium. Recombinant PTH may have a role in the management of severe hypocalcemia in children with associated gastrointestinal abnormalities, with the potential for long-term treatment for hypoparathyroidism.[11] ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Foreign Body in the Stomach of a Premature Infant

McCollough WE. J Pediatr 1962;60:277-9

This report by McCollough highlights the multifactorial etiology of bezoars in preterm infants. In contrast to swallowed foreign bodies (like coins, pins, and batteries), a bezoar in the gastrointestinal tract forms through the clumping of materials, which in normal circumstances are degraded, digested, absorbed, and easily transported.

A preterm infant of 33 weeks' gestational age received nutrition via an enteral feeding tube and suffered from pneumonia. Subsequently, hematemesis developed in the baby, and a gastric ulcer was diagnosed with radiography. Although the pneumonia resolved in the next days, oral feeding intolerance did not improve. A barium meal revealed a gastric bezoar. Conservative management, with frequent small volume milk feedings, was initiated, and the bezoar resolved spontaneously.

Predisposing factors for the development of gastric bezoars include either delayed gastric emptying or dysmotility with stasis often occurring in combination with decreased acid production. Acute respiratory distress is associated with delayed gastric emptying, and the pneumonia in this infant may have contributed to formation of the bezoar.

Dicyclomine hydrochloride, provided to the infant as a therapeutic intervention, decreases gastric acid secretion and inhibits gastrointestinal propulsive motility. Co-administered methylcellulose and aluminum hydroxide, an antacid, which can form chalky masses of aluminum phosphate precipitates, may have formed an initial nidus to promote the development of the bezoar in the stomach.

It is not clearly stated whether the baby received expressed human breast milk or infant formula. Lactobezoars in newborns fed human breast milk are described. Formula for low birth weight infants have also been purported to cause lactobezoars. Subsequent studies investigated the effects of infusion rate, volume, osmolarity, caloric density, fat, and protein composition of formulas on gastric emptying. Preterm infant formulas are now predominantly whey-based, resulting in easier digestibility and more rapid gastric emptying compared with casein-based products.

The number of reported cases of bezoar in newborns has decreased, most likely because improvements in the composition of preterm infant formula and the introduction of alternatives to antacids (histamine-2 receptor antagonists, proton pump inhibitors). However, a bezoar should still be considered in the differential diagnosis of non-bilious vomiting and food intolerance in premature infants. ■

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