

## Persistent elevated serum levels of intact parathyroid hormone after reoperation for primary hyperparathyroidism and after pamidronate therapy

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**SUMMARY:** Darcan Ş, Çoker M, Aydınok Y, Gökşen D, Özok G. Persistent elevated serum levels of intact parathyroid hormone after reoperation for primary hyperparathyroidism and after pamidronate therapy. Turk J Pediatr 2003; 45: 269-272.

Primary hyperparathyroidism is a life-threatening rare disorder. It is seen as a result of neonatal primary hyperparathyroidism, familial hypocalciuric hypercalcemia, increased vitamin D levels and inactivation of calcium sensing receptor mutations. The clinical findings are hypotonia, bone demineralization, hypercalcemia and parathyroid hyperplasia.

We present a six-month-old female patient, the first child of nonconsanguineous parents, who was referred for the investigation of failure to thrive, vomiting, constipation, fever, abdominal distention and hypotonia. Physical examination revealed weight under 3<sup>rd</sup> percentile, height 3<sup>rd</sup>-10<sup>th</sup> percentile, decreased subcutaneous fat, and distention of the abdomen. In neurological examination, hypotonia, motor-mental retardation, and active deep tendon reflexes were found. The biochemical values at the time of admission revealed primary hyperparathyroidism. Since hypercalcemia did not respond to calcitonin therapy and due to the mortality of hypercalcemia, parathyroidectomy was performed. Because hyperparathyroidism and hypercalcemia continued, angiography was done which revealed increased parathyroid hormone levels in the periphery of the innominate vein. Exploratory surgery followed, but hyperparathyroidism and hypercalcemia persisted after all of these procedures. Calcium-sensing receptor mutations and supernumerary gland were considered. Because hypercalcemia persisted, pamidronate therapy was initiated on a monthly basis.

**Key words:** hypercalcemia, hyperparathyroidism, pamidronate.

Most cases of hyperparathyroidism seen in the pediatric age group belong to the neonatal period. If hypercalcemia is unrecognized and untreated it may result in central nervous system and renal damage<sup>1,2</sup>. Hyperparathyroidism is a genetically transmitted disease of the neonate. Neonatal primary hyperparathyroidism can result from increased vitamin D and calcium-sensing receptor (CaR) mutations presenting as benign familial hypocalciuric hypercalcemia (FHH) or neonatal severe hyperparathyroidism (NSHPT). FHH has been reported to be associated with heterozygous mutations in the CaR gene, whereas NSHPT is associated with homozygous mutations<sup>1-4</sup>.

In this case report we present a 2.5-year-old patient who was considered as CaR mutation with

supernumerary parathyroid glands who did not respond to classical hypercalcemia therapy and parathyroidectomy. We achieved normocalcemia with biphosphanates, which are seldom used in infancy.

### Case Report

A six-month-old girl, the first child of nonconsanguineous parents, admitted to hospital in 1997 with vomiting, failure to thrive, abdominal distention and fever. She was born at full term after an uncomplicated pregnancy. She was hospitalized because of septicemia and dehydration when she was one month old.

Physical examination revealed an emaciated and irritable child. Her weight was 4,250

g (below 3p), and length 62 cm (3-10p) (length SDS: -1.9). She was hypotonic, and stereotypic movements, and deep tendon reflexes were hyperactive. There were no facial

(PTH level at the inferior vena cava was 591 pg/ml and 1499 pg/ml at the innominate vein), and exploration was performed. Hypercalcemia and hyperparat-hyroidism persisted after all

**Table I.** Laboratory Findings of the Patient on the First and Second Admission

	Patient's value		Normal
	First admission	Second admission	
Hemoglobin (g/dl)	10.6	9	11.5-15.5
Hematocrit (%)	32	29.4	35-45
Sodium (mEq/L)	137		134-146
Potassium (mg/dl)	4.3		3.5-6
Calcium (mg/dl)	21-32	16-17	8.8-10.8
Osteocalcin (ng/ml)	34.3	1.2	
Inorganic phosphorus (mg/dl)	7-2.8		3.8-6.5
Bone alkaline phosphatase (IU/L)	1875		145-420
Parathormone (pg/ml)	928-1230	242.3	9-65
1.25 dihydroxy calcitriol (pg/ml)	81.3		25-45
25 OH calciferol (ng/ml)	106.4		12-40
Urine calcium/creatinine ratio	1.8		0.21
Tubular phosphate reabsorption (%)	65-90		85-100

or cardiac signs of Williams syndrome. Her laboratory findings are given in Table I.

Long bone X-ray revealed distal resorption without any fractures. Pelvic, abdominal and parathyroid gland ultrasounds were normal. Based on the clinical and laboratory findings (hypercalcemia, hyperparathyroidism and hypophosphatemia), primary hyperparathyroidism was considered. In order to exclude FHH, 24-hour urine calcium excretion of her father and mother were determined as 2.1 and 1.8 mg/kg/day, respectively, while their calcium levels were 9 and 9.8 mg/dl. Initial attempts to reduce serum calcium included administration of furosemide, prednisolone and intravenous (IV) saline; however, calcium levels did not fall. Early and late phases of Tc 99m thallium and Tc 99m sestamibi scintigraphy showed physiological activity in the static images. Because continued treatment with calcitonin did not maintain normocalcemia, the patient was referred for parathyroidectomy. Four normally located hyperplastic parathyroid glands (histological examination) were removed. One gland was immediately implanted in the brachioradialis muscle of the forearm. Since postoperatively, hypercalcemia and hyperparathyroidism persisted, the implanted gland was removed, and no ectopic parathyroid tissue was found in scintigraphy. Peripheral angiography was performed and increased parathormone (PTH) levels were found in the periphery of the innominate vein

these procedures. Supernumerary parathyroid gland and CaR mutation were considered, and biphosphanate therapy was proposed, but the family refused and ceased coming for polyclinic controls while using 5 U/kg/day calcitonin.

When she admitted to our clinic two years later, her weight was 8,950 g (below 3 p) and her height was 86 cm (3-10 p) (height SDS: -1.3). She was severely hypotonic and deep tendon reflexes were hyperactive. Her laboratory findings are given in Table I. Since hypercalcemia and hyperparat-hyroidism persisted, 15 mg/m<sup>2</sup>/day pamidronate for three days was initiated. At the end of the third day serum calcium was 14 mg/dl. Monthly pamidronate therapy was initiated in order to maintain normocalcemia. At the fifth month of therapy, because serum calcium level was 9 mg/dl and PTH level was 472 pg/ml, pamidronate therapy was ceased. Although latent hypocalcemia was not observed, two months after cessation of therapy, her serum calcium level fell to 6.8 mg/dl, and calcium therapy was initiated. After pamidronate therapy, there was no evidence of hypotonia and she began active movements. Four months after cessation of therapy, she was again hypercalcemic, and pamidronate therapy at a dose of 20 mg/m<sup>2</sup>/day monthly was initiated.

## Discussion

Neonatal hyperparathyroidism is a genetically transmitted disease of the neonate and is seemingly a rare disorder. In this patient, since hyperparathyroidism and hypercalcemia persisted and did not respond to classical drug therapy and parathyroidectomy, inactivating mutations of the CaR gene mapped to chromosome 3q21-q24 was considered<sup>5</sup>. CaR gene mutations have been reported in FHH and NSHPT<sup>1,5</sup>. The diagnosis of FHH relies on decreased urinary calcium excretion with a family history of hypercalcemia or failed parathyroid surgery<sup>2,5,6</sup>. Since our patient did not show hypocalciuric hypercalcemia and her parents did not reveal hypercalcemia, FHH was excluded. NSHPT was considered based on clinical and laboratory findings.

A number of imaging tests have been developed and applied to challenge preoperative localization. Noninvasive parathyroid imaging studies include technetium Tc-99m sestamibi, ultrasound, computerized tomography (CT) scanning, and magnetic resonance imaging<sup>7</sup>. Because ultrasound and sestamibi scintigraphy failed to show the parathyroid gland, hypercalcemia persisted in spite of drug therapy and neuromuscular symptoms were evident, parathyroidectomy was performed. Hyperparathyroidism persisted after parathyroidectomy, and no apparent localizing information could be obtained with noninvasive studies. In patients with persistent or recurrent hyperparathyroidism, the chance of successful repeat surgery is reduced and the incidence of complications is greater. Therefore, maximum effort for parathyroid gland localization is made, commencing with the noninvasive procedures and proceeding to more invasive studies such as selective venous sampling<sup>4</sup>. This was utilized to localize the supernumerary glands because of persistent hyperparathyroidism after parathyroidectomy. Supernumerary parathyroid glands are found in 13% of random autopsies, are present in 30% of patients with hyperparathyroidism, and are mainly situated in the thymus, anterior mediastinum, carotid sheath or within the vagus nerve<sup>8,9</sup>. Although increased PTH levels were found in the periphery of the innominate vein and exploration surgery was performed, hypercalcemia and hyperparathyroidism persisted.

Biphosphonates are seldom used in childhood

hypercalcemia, but are used frequently in the therapy of malignant hypercalcemia. Its use in childhood persistent hypercalcemia is not widely known. Biphosphonates inhibit osteoclastic activity, and the most potent known biphosphonate is pamidronate<sup>10</sup>. Pamidronate is used in malignant hypercalcemia, bone pain due to malignancy, and in the preoperative period of primary hyperparathyroidism in adulthood<sup>11,12</sup>, while it is used in childhood leukemia, rhabdomyosarcoma, Hodgkin's disease, hepatoblastoma, neuroblastoma, Ewing sarcoma<sup>10</sup>, symptomatic therapy of Paget's disease, McCune-Albright syndrome and osteogenesis imperfecta<sup>12-16</sup>. Prompt resolution of hypercalcemia was achieved in an 11-year-old renal post-transplant patient by single dose of 0.5 mg/kg/d pamidronate. In 14-year-old male patient on peritoneal dialysis with tertiary hyperparathyroidism, a single dose of pamidronate (0.4 mg/kg) achieved resolution and prolonged control of hypercalcemia<sup>17</sup>. One or two intravenous doses of disodium pamidronate (35-50 mg/m<sup>2</sup>) resulted in normalization of plasma calcium concentration within two to four days in four children with end-stage hepatic failure<sup>18</sup>.

Since hypercalcemia in our patient did not respond to classical therapy and parathyroidectomy, pamidronate therapy was initiated. No adverse effects of pamidronate therapy, such as fever, thrombocytopenia, hypophosphatemia or renal function failure, was seen in our patient.

As a result, pamidronate can be used in primary hyperparathyroidism where parathyroidectomy is not sufficient, in addition to its proven usage in malignant hypercalcemia, osteogenesis imperfecta and Paget's disease.

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