Elmer Press Case Report Int J Clin Pediatr. 2014;3(3):94-96

Severe Hypercalcemia Due to Primary Neonatal Hyperparathyroidism in an 8-Day-Old Neonate: A Case Report

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Abstract

An 8-day-old boy was referred to our hospital because of poor feeding and hypotonia from the second day of his life. Investigations in our hospital showed marked hypercalcemia due to primary hyperparathyroidism (PHPT). Intensive medical treatment was unsuccessful and he was cured after total parathyroidectomy had been performed. It seems that total parathyroidectomy is the treatment of choice in cases of neonatal PHPT.

Keywords: Calcium level; Parathyroid hormone; Hyperparathyroidism

Introduction

Diseases of the parathyroid glands in pediatric patients constitute a rare group of conditions that have significant morbidity [1]. Primary hyperparathyroidism (PHPT) in childhood and especially neonates with an estimated incidence of around 2-5/100,000 is so rare that it often misses the trained eye of pediatrician until irreversible organ damage has occurred [2-4]. Neonatal hyperparathyroidism is defined as symptomatic hypercalcemia with skeletal manifestations of hyperparathyroidism in the first 6 months of life. It often presents in the first few days of life with severe PTH-dependent hypercalcemia, hypotonia, irritability, failure to thrive, constipation and respiratory distress [5]. The main forms of primary familial hyperparathyroidism presenting in infancy are: 1) autosomal recessive familial parathyroid hyperplasia [6, 7]; 2) autosomal dominant familial hypocalciuric hypercalcemia (FHH) [8], resulting from an inactivating mutation of the calcium sensing receptor (CaSR) gene; 3) neonatal severe hyperparathyroidism (NSHPT) in children with homozygous or double heterozygous mutations of CaSR gene; and 4) sporadic neonatal hyperparathyroidism due to *de novo* heterozygous CaSR mutations [9]. Most of the literature on PHPT in pediatric patients has been limited to case reports and small series. There are very few single center reports available which talk about its presence [10]. About 50 neonates with neonatal primary hyperparathyroidism (NPHP) have been reported and it has been suggested as a possible contributor to a small number of cases of the sudden infant death syndrome [11]. All reported cases of NPHP have been due to parathyroid chief cell hyperplasia [12]. The authors report an 8-day-old boy with severe hypercalcemia due to PHPT, and discuss the importance of this rare endocrinology disease.

Case Report

An 8-day-old boy was referred to our hospital for poor feeding and hypotonia from the second day of his life. He was a full-term baby, born with appropriate Apgar score. He was born to a multipar mother in cesarean section because the other baby was a healthy girl that was born in cesarean section. His birth weight was 3,500 g, with birth head circumference of 34 cm. The baby was a product of a consanguineous marriage with normal birth history. Physical examination showed a term baby that was extremely hypotone and had decreased neonatal reflexes.

Investigation in our hospital showed marked hypercalcemia 35 mg/dL (8 - 10 mg/dL), phosphate 3.4 mg/dL (4.5 - 6.5 mg/dL), alkaline phosphatase 487 IU/L (115 - 960 IU/L), magnesium 2 mg/dL (1.2 - 2.2 mg/dL), parathyroid hormone (PTH) intact molecule 640 pmol/L (17.3 - 73), vitamin D-25, 4 ng/mL (deficiency < 10). Additionally urine Ca excretion was 10 mg/kg/day. Thyroid function test, serum electrolytes, urea, creatinine and liver function tests were normal. Evalu-

Manuscript accepted for publication June 26, 2014

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doi: http://dx.doi.org/10.14740/ijcp126w

ation of mother for serum levels of Ca, P and PTH showed normal values. Skeletal survey showed generalized osteopenia, with evidence of subperiosteal bone resorption. Ultrasound of the kidneys showed increased echogenicity of both kidneys with a minimal enlargement in kidneys size while there was no evidence of nephrocalcinosis. Echocardiography showed normal left ventricular function, with mild tricuspid regurgitation. Combination of clinical, laboratory and radiological findings was consistent with the diagnosis of neonatal PHPT. Due to the extremely high concentration of calcium, vigorous treatment with saline normal, furosemide, hydrocortisone, intravenous pamidronate 1 mg/kg/day, and calcitonin was started immediately. Unfortunately, serum calcium concentration did not drop significantly (serum Ca decreased to 27 mg/dL after treatment). Since patient did not respond to the medical therapy and his symptoms persisted, surgical approach was considered. On the 11th day of his life, total parathyroidectomy, thymectomy and mediastinal explore were done successfully. Five specimen were excised for histological study that only one specimen was identified as thymus gland. The excised parathyroid glands histology was consistent with generalized hyperplasia. After 3 days of the surgery serum Ca level dropped to 11.5 mg/dL, while PTH level decreased to 120 pmol/L (17.3 - 73). Calcium supplement and activated form of vitamin D were started on the first week of post operation. The postoperative course was complicated by septicemia with Klebssiella that resolved with antibiotic and intravenous immunoglobin administration. By the end of the fourth postoperative week, serum calcium level was in normal range while receiving oral calcium supplement.

Discussion

PTH is the chief regulator of calcium homeostasis in the human body. PHPT results from inappropriate overproduction of PTH from one or many parathyroid gland(s) and presents with hypercalcemia. NPHP is a rare disease, which is often fatal [12]. Usually symptoms manifest in the first days after birth [13]. Symptoms include poor feeding, irritability, constipation, polyuria, hypotonia, respiratory distress and bone abnormality such as osteopenia, subperiosteal bone resorption, pathologic fracture and failure to thrive almost in all cases. It is important to differentiate primary from secondary and tertiary hyperparathyroidism. Secondary hyperparathyroidism occurs as a normal response to hypocalcemia due to diseases affecting the kidney (such as renal tubular acidosis), liver, intestines, and vitamin D deficiency. In newborn infants, maternal hypoparathyroidism with hypocalcemia, maternal pseudohypoparathyroidism, and rare genetic and metabolic syndromes can lead to secondary hyperparathyroidism. Tertiary hyperparathyroidism occurs in patients with long-standing secondary hyperparathyroidism who develop autonomous PTH production with hypercalcemia. The most common situation resulting in tertiary hyperparathyroidism is the patient with secondary hyperparathyroidism with renal failure who then receives a renal allograft [14, 15].

Parathyroid hormone elevation can occur due to causes other than PHPT in patients with normal blood calcium levels. The most common cause is chronic kidney disease, but other causes include vitamin D deficiency, medications (such as lithium and thiazide diuretics), and FHH due to a heterozygous mutations of the CaSR gene. The latter can be reasonably differentiated from PHPT based on the calcium to creatinine clearance ratio of less than 0.01 (mmol:mmol) with 85% sensitivity and 88% specificity [16].

The choice of therapy in PHPT varies from conservative medical management to total parathyroidectomy with or without autotransplantation based on the severity of the disease [17].

The cornerstones of medical management include bone protection with the use of bisphosphonates and lowering of calcium level with calcimimetics. Multiple studies have shown that bisphosphonates improve bone mineral density [18]. Calcimimetics, like cinacalcet, are designed to allosterically modify the CaSR, thus sensitizing it to circulating calcium levels and down regulating PTH transcription, secretion, and parathyroid cell proliferation [19].

Medical therapy without surgical intervention has a mortality rate of 70-87% and severe long-term complications in the survivors [13]. As these patients with severe hypercalcemia are almost always critically ill and responses to medical treatment are usually poor, surgical approach as the major option for definite treatment should be considered.

Our mentioned case did not respond properly to intensive medical treatment, so he was gone under a total parathyroidectomy. Three possible surgical procedures for these patients are: total parathyroidectomy, subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. Total parathyroidectomy leads to hypoparathyroidism with a life-long need to calcium and vitamin D supplementation. In total parathyroidectomy with autotransplanttation all four parathyroid glands are removed and a small portion of a gland is implanted into intramuscular pockets. As the treatment of our patient with total parathyroidectomy was successful and life saving since severe hypercalcemia in our case could be lethal, it can be concluded that this surgery successfully regulated calcium homeostasis in severe primary hyperparathyroidism.

Conclusion

Though NPHP is a rare disease, pediatricians should be aware of this potentially fatal disorder. This disorder is accompanied by severe hypercalcemia that is generally not responsive to medical treatment. It seems that total parathyroidectomy is the treatment of choice in cases of NPHP.

Conflict of Interest

We admit that there is not any sponsor responsible for the writing of the report and the decision to submit the manuscript for publication. We also state that the first draft of the manuscript was written by corresponding author of the article and no one was paid to produce the manuscript.

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