Severe neonatal hypercalcemia in 4-month-old, presented with respiratory distress and chest wall deformity

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Abstract
Neonatal severe hyperparathyroidism (NSHPT) is a rare disease affecting calcium metabolism and results in severe life-treating hypocalcemia of the neonates. Diagnosis can be challenging due to variable and nonspecific symptomatology. We are reporting on a 4-month-old female infant presenting with respiratory distress and chest wall deformity. We are trying to highlight different surgical options for this rare disease and importance of close collaboration with the pediatric endocrinologist in the treatment plan for those patients.

1. Case report

We are reporting a 4-month-old female infant admitted to the pediatric unit at King Fahad Hospital of University of Dammam with respiratory distress and chest wall deformity. She has bilateral concave deformities of the rib cage on the lateral side with costal margin retraction giving her a bell-shaped chest (Fig. 1). This deformity was associated with paradoxical movement of the chest wall during breathing. Her initial chest x-ray revealed bilateral pulmonary infiltration and marked demineralization of the chest wall skeleton. The infant patient was started on intravenous antibiotics and oxygen supplementation to treat the bilateral pneumonia. She had a complete workup including serum electrolytes; calcium and vitamin D levels were all within normal ranges. The family reported that the patient was admitted to another hospital outside the country at the age of 20 days with dehydration, lethargy, and decreased feeding. Her bloodwork at that time showed elevated serum calcium levels at 8.3 mmol/L (ref 2.2–2.6) and normal 25-OH vitamin D at 12.2 ng/ml (ref 10–100). Her hypercalcemia was treated at that time with rehydration, low calcium formula, Lasix, and intravenous hydrocortisone. This regime continued until her calcium level normalized. Then, the patient was discharged home at age of 33 days on low calcium formula only. The family also reported that

Abbreviations: ADH, autosomal dominant hypocalcemia; CaRS, calcium-sensing receptors; FHH, familial hypocalciuric hypercalcemia; T4, Free Thyroxin; iPTH, Intact Parathyroid hormone; NSHPT, neonatal severe hyperparathyroidism; PICU, pediatric intensive care unit; SNHPT, Serum thyroid stimulating hormone; TSH, severe hyperparathyroidism.

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one of her cousins had hyperparathyroidism at the age of 9 months that required a total parathyroidectomy.

At this time, the patient was admitted as pneumonia and systemic antibiotics started with supplemental oxygen. The endocrine team was consulted and an endocrine workup was ordered. Serum thyroid stimulating hormone and T4 were normal. Calcium levels were normal 9.0 mg/dl (ref. 9–11). Phosphorus was low 1.9 mg/dl (ref. 2.5–4.9), but iPTH was very high 131 pmol/L (ref. 1.5–7.2). Repeat PTH confirmed the high levels at 109 pmol/L. The patient had an ultrasound on her neck that showed normal thyroid and none of the parathyroids were visualized. At that point, a clinical and laboratory diagnosis of NSHPT was made. After improvement of her lung function, the patient underwent a total parathyroidectomy through a collar neck incision with autotransplantation of one-third of a gland in the right sternomastoid muscle. Another parathyroid gland was cryopreserved in our tissue bank. An intraoperative frozen section confirms that all 4 specimens were parathyroid tissues. Permanent histology revealed diffuse hyperplasia of the parathyroid tissue. Postoperatively the patient was admitted to the PICU, was kept on a calcium gluconate infusion, and checked for serum calcium every 12 h. Post operative iPTH level was undetectable. Episodes of hypocalcaemia were treated with calcium gluconate bolus over 15 min and a slow increase in the infusion rate. Maximum intravenous calcium infusion was 400 mg of ca/kg/day. Over the course of days, the patient slowly advanced to feed and oral calcium and vitamin D supplementation increased as the infusion decreased at day 13 postop patient was off calcium infusion, at that time Serum iPTH was detectable. On day 15 postoperatively, the patient suddenly developed progressive neck swelling. An urgent neck ultrasound was performed and showed fluid collection. The patient was shifted to the operating room were she was explored under anesthesia. Neck hematoma was evacuated and obvious bleeding was identified. After few days in the PICU, the patient was transferred to the ward on oral calcium supplementation. At a 2-month follow-up, the patient was doing better with active calcium level ranges between 7 and 9 mg/dl. Few months postoperatively patient was on and off calcium supplementation with high calcium formula. At age of 9 months patient serum calcium level maintained at low normal value on oral calcium supplementation, iPTH level is detectable at lower than normal value 1.11 pmols/L reference range (1.58–7.2).

2. Discussion

Neonatal Sever Hyperparathyroidism is a rare disorder caused by inactivation mutations of the extracellular CaRS. These receptors are expressed in many tissues including parathyroid glands, renal tubular cells, and parafollicular cells of the thyroid gland and bones. These receptors regulate and maintain calcium hemostasis [1–3]. Single mutation of the CaRS gene results in FHH, a benign disease that may result in mild asymptomatic hypercalcemia that requires no specific treatment. It is thought that a homozygous mutation will result in NSHPT, a severe form of hypercalcemia that presents usually in the first few weeks of life. On the other hand, activation mutation of the CaRS genes results in ADH [4].

Hypercalcemia in NSHPT is usually very severe and can be fatal. Diagnosis of SNHPT is usually challenging; patients can present with very non-specific symptoms such as lethargy, seizures, hypotonia, respiratory distress, failure to thrive, and/or dehydration. High index of suspicion is a key for early diagnosis. Failure to establish diagnosis early may result in significant complications such as neurodevelopment delay, skeletal deformities, renal failure, and nephrocalcinosis. Serum calcium levels are usually elevated but can be normal such as our patient’s were. Elevated serum intact parathyroid hormone level is usually diagnostic. Serum phosphate levels are usually low and the vitamin D level (25-OH cholecalciferol) is usually normal as well. Neck imaging in the form of ultrasound or nuclear scan is usually not helpful and may delay the definitive treatment [5]. Renal ultrasound can be helpful in detecting nephrocalcinosis.

Treatment of SNHPT can be classified into three stages. The first stage includes acute stabilization of the patient. Intravenous fluid resuscitation is the mainstay of treatment. Intravenous pamidronate is a useful adjunct if hypercalcemia persists, it reduces the bone resorption. More recently, calcimimetics agents such as cinacalcet have been used successfully in some cases of NHPT. Cinacalcet increases CaRS affinity to calcium, which improves the function of the mutant receptors and subsequent decrease in parathyroid hormone secretion [6,7]. Wilhem-Bals et al. described successful use of cinacalcet for 6 years with incremental increase of dose. Cinacalcet may work in some mutations but not all [6]. The second stage of treatment is the definitive treatment of NSHPT. Surgery remains as the most effective intervention that is associated with better long-term calcium level stabilization [5,8]. Surgery may vary from total parathyroidectomy with or without autotransplantation and 3.5 glands removal. Al-Shanafey et al. [5] reported the biggest series from one center where 5 patients underwent total parathyroidectomy with auto transplant on half a gland in the forearm. A follow-up of 1–9.5 years showed that all were alive and 4 of them required calcium and vitamin D supplementation. One of the patients had failure of an autotransplanted graft and none of them developed graft dependant hypercalcemia. Total parathyroidectomy without autotransplantation was tried on early practice with good initial control of the disease but lifelong hypocalcaemia and calcium supplementation was invariably needed [9,10]. Cryopreservation of the removed parathyroid glands can be useful in this disease. The preserved glands can be used if the initial autotransplantation was not successful [11] or banked for future research and genetic testing. The third stage of treatment is postoperative control of severe hypocalcaemia and bone hunger. Our patient required a significant dose of calcium infusion ranging between 200 and 400 mg/kg/day of elemental calcium together with vitamin D supplementation. An episode of hypocalcaemia can be treated with intermittent boluses. Correction of magnesium and phosphate is needed.
After 2 weeks, the total calcium requirement slowly decreased and the patient transitioned to oral calcium supplementation. We believe that close monitoring in an intensive care unit post-operatively is needed given how fragile infant patients are.

3. Conclusions

NSHPT is a rare disease that requires a high index of suspicion and very good history to make an early diagnosis and avoid complications. Medical treatment is helpful in stabilizing the patient and bridges him or her to the definitive surgical treatment once the overall condition has improved. We believe that total parathyroidectomy remains the most effective long-term treatment. Heterotrophic parathyroid autotransplantation of one-quarter or one-third of a gland might save the patient from long-term calcium supplemenations. Cryopreservation of one of the glands during the initial procedure can be helpful should the transplanted gland not take. Admiring the retrospective and relatively small numbers of case series that have been reported, more studies with longer follow-up periods are needed to understand the disease nature better and compare different surgical options.

Disclosure

The author has nothing to disclose.

References