

Neonatal Primary Hyperparathyroidism

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ABSTRACT

Primary hyperparathyroidism in neonate is extremely rare and fatal. It can also result in several sequelae if not promptly recognized and surgically corrected as soon as possible in early life. It is usually presented with symptoms of chronic hypercalcemia, such as irritability, hypotonia, constipation, poor feeding and respiratory distress with some sorts of hypercalcemic crisis. They often develop polyuria and dehydration associated with failure to thrive.

Abbreviation: NPHPT; neonatal primary hyperparathyroidism. PTH; parathyroid hormone. FBHH; familial benign hypocalciuric hypercalcemia. CASR; calcium-sensing receptor. NSHPT; neonatal severe hyperparathyroidism. KHMC; King Hussein Medical Centre. BP; blood pressure. Ca; Calcium. P; Phosphorus. ALP; Alkaline phosphate. U Ca/Cr ration; Urine Calcium Creatinine ratio.

CASE PRESENTATION

A 4 week old female neonate with body weight of 2.6 Kg was referred to pediatric Endocrinology Clinic at KHMC and admitted for poor feeding, irritability and attacks of apnea with respiratory distress. Diagnosis of neonatal primary hyperparathyroidism with markedly hypercalcemia was considered. Parathyroidectomy with auto-transplantation of one gland was considered after failure of medical therapy. Two months after surgery, the patient became off treatment and her calcium level controlled.

INTRODUCTION

Neonatal primary hyperparathyroidism is extremely rare disease in the first six month of life. Nearly fifty cases reported in the world, with various causes. It is thought to be autosomal recessive disease due to mutation of the calcium-sensing receptor gene^{1,6}, in which the inhibitory effect of extracellular calcium on the secretion of PTH by chief cells is absent^{2,7}. Most reported cases have been seen in term infant and total parathyroidectomy may be life saving for severely affected infant; so mortality associated with surgical treatment is nearly four times less than medically managed patient^{1,8} although new medical – therapies are under investigation. Recent report has demonstrated the effectiveness of pamidronate therapy in severe neonatal hypercalcemia which allows parathyroidectomy to be delayed until the condition of the baby is stable for surgery^{2,3}.

CASE PRESENTATION

Four weeks old female neonate was referred to our paediatric clinic at KHMC due to, Poor feeding, irritability and attacks of apnea. She was born to a 29 years old woman, smooth and uneventful pregnancy, at 39 weeks gestational age. She was born to a healthy first degree cousin parents who has another healthy son who is four years old. At age of three weeks the baby suffered from poor feeding, irritability and attacks of apnea with respiratory distress. After several visits to an out patient clinic, she was admitted to the local hospital as a case of neonatal sepsis, where septic work up was done including lumbar puncture and was covered with broads spectrum antibiotics. All cultures result were negative, other lab test were normal except hypercalcemia where serum calcium level=21.6mg/dl (NR=8.6-10.5mg/dl). The test was repeated twice on the same day but the result was nearly the same, and so started to correct hypercalcemia with hyper-hydration using diuretics and hydrocortisone. The calcium remained between (16.7-18.6mg/dl). There after referred as case of resistant hypercalcemia.

At age of four weeks her weight was 2.6kg, hypoactive, constipated, abdominal distension and respiratory distress, her vital signs were as follow; Respiratory rate (40-50/minute), heart rate =140/minute, temperature 37c axillary, BP=75/55mmHg. With moderate dehydration, subcutaneous fat loss with muscle wasted. Biochemical tests at presentation and after surgery are shown in table1. Skeletal survey showed osteopenia and bone demineralisation Abdominal ultrasound showed medullary nephrocalcinosis. 2D Echocardiography showed normal study and 99-Tc-sesta MIBI showed four parathyroid glands in anatomical position with homogenous radio-tracer up-take.

Initial management started with super-hydration with normal saline, diuretics and vitamin D 400iu/day. The possibility of primary hyperparathyroidism was elicited in the top of differential diagnosis. The result after few days of aggressive treatment showed in figure 1, when the calcium still high and surgery not permissible, so a trial of pamidronate was introduced of 1mg/kg/day for 4 days proved effectiveness. Her condition was stabilized and total parathyroidectomy with auto-transplantation was successfully performed. Immediately (12 hours) after the surgery calcium level dropped to 6.9mg/dl and PTH to 28pg/ml. So calcium and vitamin D supplementation was given. The calcium rose to the normal range showed in figure 1. The treatment was kept for 6 weeks post-operatively, then stopped gradually with close monitoring of calcium which showed normal level of calcium and phosphorus. At age of one year the baby growth was at 10th-25th centile regarding to her weight and length, also her development catch-up and bones re-mineralized adequately.

Figure 1: Calcium and Phosphorus levels monitoring before and after surgery.

Table 1: Biochemical result of the patient before and after surgery.

Biochemical test	Pre-surgery	Post-surgery
Ca (NR: 8.5-10.2 mg/dL)	21.6 mg/dL	9.6 mg/dL
P (NR: 3.5-6.5 mg/dL)	2.5 mg/dL	5.8 mg/dL
ALP (NR: 90-270 U/L)	683 U/L	370 U/L
PTH (NR: 12-65)	635 pg/mL	28 pg/mL
U Ca/Cr ratio (<0.86 mg/dL)	1.8 mg/dL	0.53 mg/dL

DISCUSSION

As known the primary hyperparathyroidism occurs extremely rare in neonate. Just few dozen of cases are reported till now, but many cases were reported in infants who were born to untreated hypoparathyroidism mothers during pregnancy who have had bony demineralization, which consistent with secondary hyper-parathyroidism. These cases are less severe and have less complication with normal range of bone profile, but they have high to normal level of PTH. On the other hand the mother screening for all bone profile and PTH level are low⁴. In our case the screening of the mother was normal and no history of tetany noted during pregnancy.

Familial benign hypocalciuric hypercalcemia (FBHH) is one of the commonest causes of hypercalcemia. It is a benign condition of autosomal dominant life-long hypercalcemia, with few if any complication and normal longevity. It is usually characterized by mild hypercalcemia, inappropriately normal PTH levels, hypocalciuria with absence of classical skeletal and renal complication of hypercalcemia. But polyuria, weakness, headache and mental problems are associated symptom^{3,5}, in the contrast (NSHPT) present as dramatic highly morbid condition if untreated. It is life-threatening disease characterized by severe hypercalcemia, high PTH with parathyroid hyperplasia, hypotonia, respiratory distress and bony demineralization. Whereas cases in the earlier series died if untreated and survived post-parathyroidectomy^{5,6}, other causes of hypercalcemia in neonate and infancy must be considered in differential diagnosis such as; idiopathic infantile hypercalcemia, vitamin D intoxication, and William syndrome. Some reported cases of hypercalcemia occurring in sibling; however some cases suggestion of inheritance manner. In our case regarding to the clinical presentation, negative family history and absence of molecular study the inheritance is not conclusive, since variable pen trance can happened. Mutation in the calcium-sensing receptor (CASR) gene which go to loss of function of these receptors can be seen in both FHH and NPHP. Activation of CASR by extracellular calcium inhibits secretion of PTH by the chief cells⁷. The management of NPHP remains challenging when medical therapy is inadequate and surgical intervention must be undertaken as soon as possible to prevent the serious irreversible long term complication. As in our case many other reports advise that treatment of choice is total para-thyroidectomy with auto-transplantation, it is life-saving and mortality rate is 4 times less than medical therapy^{6,8}. Others like Ross et al reported that seven of eight patients treated medically for primary hyper-parathyroidism died in infancy, with a mortality rate of 87%, but those treated surgically was reduced to 24%⁹. It was not easy to prepare the critically ill patient for para-thyroidectomy. Initially we start with medical management such as hyper-hydration, furosemide, steroid and pamidronate as in our case the hypercalcemia was resisted until we induce pamidronate 1mg/kg/day for 4 days. Then the calcium levels dropped to normal range before surgery without side effect, but it was not enough to control hypercalcemia completely¹⁰. For surgical procedures there are three possibility: total para-thyroidectomy, subtotal para-thyroidectomy and total para-thyroidectomy with auto-transplantation. The first option needs life long supplement with calcium and calciferol. Excellent result obtained from total para-thyroidectomy and auto-transplantation as in our patient.

CONCLUSION

Neonatal primary hyper-parathyroidism is fatal and extremely rare .It must be considered in differential diagnosis in cases of hyper-calcemia in 1st six month of life. Early detection and surgical total para-thyroidectomy and auto-transplantation is life-saving and prevent irreversible sequale.

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