CASE REPORT

Neonatal severe hyperparathyroidism: A case report

Mahmood Shaukat,[1] Hafiz Mahmood Ahmad,[2] Muhammad Umar Shafiq[3]

Abstract

Neonatal severe hyperparathyroidism (NSHPT) is a rare genetic disorder that presents within the first six months of life. We present the case report of a male child who presented to us in the first month of his life with symptoms of lethargy, constipation, and reluctance to feed. One sibling of the child had died earlier with similar symptoms in the first six months of life. Upon physical examination, the child was lethargic, dehydrated, had bradycardia with hyperreflexia. Serum electrolyte analysis showed hypercalcaemia and hypophosphataemia. Further workup revealed elevated serum parathyroid hormone levels and Calcium sensing receptor (CaSR) gene mutation in autosomal recessive patterns. The father was discovered to be heterozygous for the same mutation but is asymptomatic. Diagnosis of neonatal severe hyperparathyroidism was made and the child was managed medically with intravenous fluids, Furosemide, Pamidronate, and Cinacalcet. On inconsistent response to medical therapy, he underwent total parathyroidectomy with auto transplantation of half of the left lower parathyroid gland. Postoperatively, the child is being managed on oral calcium and Alpha Calcidiol supplementation and is doing well.

Keywords: Neonatal severe Hyperparathyroidism, Serum Calcium, Parathyroid Hormone level, Parathyroidectomy.

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Introduction

Neonatal severe hyperparathyroidism is a rare genetic disorder which presents within first 6 months of life usually with symptoms of lethargy, hypotonia, reluctance to feed, polyuria, gastrointestinal disturbances, osteopenia, poor feeding and respiratory distress.[1] It can be fatal if not diagnosed and managed timely. We present case report of a male child who presented with neonatal hyperparathyroidism and discuss our approach to diagnosis and treatment. Informed written consent was taken from patients' father for publication of case report.

[1]Department of Paediatric Surgery, Ramzan Ali Syed Hospital, Lahore, [2]Department of Paediatric Surgery, King Edward Medical College, Mayo Hospital, Lahore, [3]Department of Paediatric Medicine, Civil Hospital, Bahawalpur, Pakistan.

Correspondence: Hafiz Mahmood Ahmad. Email: meh_ahd@hotmail.com

Case Presentation

A male child born of consanguineous marriage presented to the paediatrician at the age of 16 days with the complaint of lethargy, constipation, and reluctance to feed. He was born via LSCS due to placenta previa at 35th week of gestation. At birth, his weight was 2kg. He is the third born of the family. He remained in the well-baby nursery for two days after birth and was discharged uneventfully. He was breastfed and got BCG vaccination on the second day of life. He remained well for the first 15 days when he developed symptoms of lethargy, constipation, and reluctance to feed. He presented to a local paediatrician with these symptoms, who suspected meningitis and got his lumbar puncture done. Cerebrospinal fluid (CSF) examination was noted to be normal. The child was then referred to one of the authors at Surgicare Complex Bahawalpur on January 19, 2021.

The firstborn of the family was a male who died within the first six months of life due to similar complaints. The second born is a healthy female.

Upon physical examination in Bahawalpur, the child was lethargic and dehydrated. He had cold, clammy skin and was hypotonic. The child had bradycardia and hyperreflexia. His heart rate was 56/min which generated suspicion of electrolyte disturbances. The chest was bell-shaped but air entry was clear bilaterally. The abdomen was soft and non-tender. Weight at presentation was 2kg. Facial features were normal.

His serum electrolyte profile was obtained which showed hypercalcaemia, serum calcium level 22.6 mg/dl (Normal=N 9-11mg/dl), while Serum Sodium, Potassium, Chloride, and Bicarbonate levels were normal.

Further investigations included skeletal survey, serum phosphate, vitamin D, serum magnesium, serum phosphate, and parathyroid hormone levels.

A skeletal survey showed reduced bone density, metaphyseal fractures in the lower end of both femurs and upper ends of the tibia. There was crowding of upper ribs (1-5th).

Vitamin D level was 20.9ng/ml. His serum phosphate level was 2mg/dl (N:3-6.9 mg/dl). Serum magnesium level was 1.7mg/dl (N:1.7-2.7mg/dl). Urinary Calcium level was not

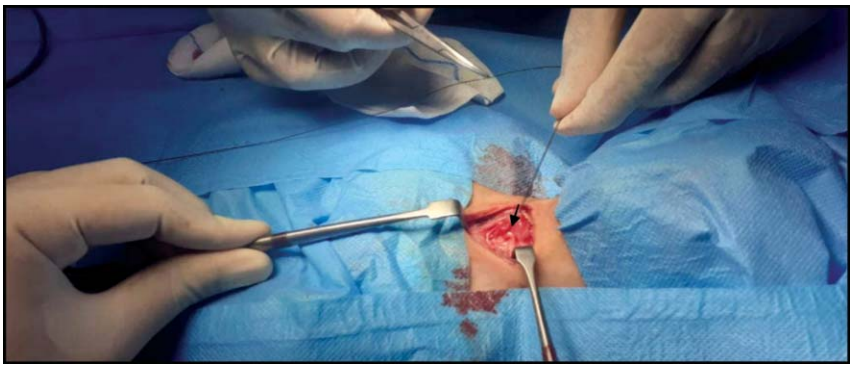

Figure: Arrow pointing at the right lower parathyroid gland in the picture. Stitch is retracting the right lobe of the thyroid gland medially.

measured. Serum Parathyroid hormone (PTH) level was 1468.5pg/ml (N:15-65pg/ml).

On discovering hyperparathyroidism as the cause of hypercalcaemia, ultrasound of the neck and sestamibi scan were done to locate the parathyroids and find any adenoma. The parathyroid glands could not be localised by an ultrasound scan. Sestamibi scan did not show any radiographic evidence of parathyroid uptake. No evidence of parathyroid adenoma was discovered.

The patient was managed medically on injection (inj) Pamidronate, tablet (tab) Cinacalcet 3mg PO BD to decrease serum calcium levels, full maintenance intravenous (IV) fluid concerning weight, and Furosemide 1mg/kg IVBD to avoid nephrocalcinosis. His serum PTH level was reduced to 444 pg/ml pre-operatively. Serum calcium reduced to 9.2mg/dl and rose again to 17.37mg/dl preoperatively. The child was discharged on tab Cinacalcet 3mg PO BD, tab Spiromide 1mg PO BD and was referred to us on the same day.

The patient presented to us on the 41st day of life on February 15, 2021. His total parathyroidectomy was done after obtaining informed consent from the parents. The child was put in supine position with neck extended and total parathyroidectomy with implantation of half of the left lower parathyroid in the left sternocleidomastoid was done on February 16,2021. Parathyroids were approached laterally after mobilising the sternocleidomastoid on either side. The right and left lobes of the thyroid were retracted medially after taking vicryl stay sutures through them. Parathyroids were identified as pink structures in relation to the recurrent laryngeal nerve (RLN) with no surrounding fat, unlike in the adults, where it is more yellow with surrounding fat. All parathyroids were separated, carefully preserving the RLNs on both sides. Only visual magnification was used. No intraoperative radiotracer uptake or frozen section was used due to non-availability and financial limitations.

At the time of extubation, both vocal cords were noted to be normal. Postoperative serum PTH level was obtained which was reduced to 3.5pg/ml(N:18.5-88pg/ml).

The child developed carpopedal spasm postoperatively in the first30 minutes and was loaded with 4mg of 10% calcium gluconate which was continued on 4mg IV eight hourly infusions in maintenance fluid on 0 post-op day which was reduced to 2mg IV eight hourly on first POD and 1mg IV eight hourly on the second postoperative day. The child was given full maintenance fluid during this time with injection of Furosemide 1mg/kg. Urine output was strictly monitored hourly and was maintained at 2cc/kg/hour. ECG monitoring was done in this duration via cardiac monitor. Oral feed was started four hours after the operation. Calcium level decreased to 13.64mg/dl on second postoperative day. The child was discharged on serum calcium P 1cc PO TDS and Alpha Calcidiol drops 0.2mcg/day on third post-op day. No hoarseness of voice was observed at the time of discharge. On the seventh postoperative day, serum calcium was 9.1mg/dl (Normal: 9-11mg/dl).

Biopsy confirmed that all four parathyroid glands have been removed. Clear cell hyperplasia was noted in parathyroid glands on biopsy.

After four months, serum PTH level was 4pg/ml (N:18.5-88 pg/ml).

Discussion

NSHPT is a type of familial hypercalcaemic hypocalciuria (FHH) which is caused by an autosomal recessive non-activating mutation in CaSR located majorly in chief cells of the parathyroid, bones, and epithelial linings of renal tubules.[1] Almost 200 types of mutations of the CaSR gene have been described which include both activating and non-activating mutations. Their penetration in autosomal dominant or autosomal recessive patterns dictates whether the individual will have FHH or NSHPT.[2] Genetic mutations for NSHPT are mostly located on 3p13.3.[3] In our case, genetic analysis confirmed the presence of the mutation in CaSR. Variant c.295 G>C p. (Asp99His) causing an amino acid change from aspartic acid (Asp) to Histidine (His) at position 99 was identified in the child in autosomal recessive pattern and in the father in heterozygous pattern. The mother's genetic analysis was recommended but was not performed on the family's

wish. The child's mother had a history of hypercalcaemia while the father is asymptomatic.

Patients with NSHPT usually present within the first six months of life and mostly within the first few weeks.[4] Most of these children present with signs and symptoms of hypercalcaemia and hyperparathyroidism which include lethargy, reluctance to feed, hypovolaemia, polyuria, hypotonia, gastrointestinal motility disorders, and respiratory difficulties, and if proper diagnosis is not made, the disease can be fatal in 50% cases.[4] Our patient presented with lethargy, reluctance to feed, and constipation. On examination, hypotonia, bradycardia, and dehydration were noted. One elder sibling had been lost due to lack of proper diagnosis.

NSHPT is characterised by markedly elevated serum parathyroid hormone levels, hypercalcaemia, hypophosphataemia, hypocalciuria. Features of elevated parathyroid hormone levels, hypercalcaemia, and hypophosphataemia were present in our case. While considering the diagnosis of hypercalcaemia in infants, it is also important to rule out other causes such as iatrogenic hypercalcaemia, vitamin D intoxication, William syndrome, FHH, and idiopathic infantile hypercalcaemia. All these scenarios can lead to almost similar presentations but can be differentiated further on detailed work up, as was done in this case.[5]

NSHPT can be treated medically or surgically. Medical treatment includes excessive IV fluids and various drugs like loop diuretics such as Furosemide, Bisphosphonates such as Pamidronate, Calcitonin, and Calcimimetic such as Cinacalcet.[6] Recently, a case has been described where it was used as monotherapy to control hypercalcaemia in a premature infant. It improved serum calcium levels and bone density on X-rays.[6] Cinacalcet is mostly used as an adjunct therapy to intravenous fluid and Bisphosphonates but it has proved to be efficacious in selected cases as monotherapy as well. It does decrease serum parathyroid hormone level and helps in bone healing but calcium levels remain on a bit higher side or levels keep on fluctuating. Cinacalcet can be given at the dose of 0.4mg/kg/day and can be increased to 9.6mg/kg/day in two to three divided doses to create an effective response.[6] Pamidronate which is a Bisphosphonate has also been used in 20mg/m^2 to 30mg/m^2 dose to control hypercalcaemia in junction with hyperhydration and diuretics.[7] We used a combination of all these drugs in our case which did decrease the serum calcium and parathyroid hormone level but the response was not optimal and consistent. Serum calcium level dropped initially with medical management but rose again.

However, in refractory cases and to avoid long-term irreversible complications such as nephrocalcinosis, cardiac abnormalities, and neurological changes, surgery remains the ultimate treatment as was done in the present case.

The most important step for surgery is the localisation of parathyroid glands. To localise the parathyroid glands exactly, various investigations such as ultrasound of the neck, MRI, and sestamibi scan can be used. Sestamibi scan is most sensitive (88%) and most specific (97%).[8] However, studies indicate failure of all investigations including sestamibi scan to exactly localise ectopic glands,[8] such as in this case because the cause here was hyperplasia of all parathyroid glands. On table injection of Methylene blue can be used to locate parathyroid glands but different studies have different opinions about it.[8] Methylene blue was not used in this case because almost all the preparations of Methylene blue were produced locally and none had the exact strength described on it. So the dose for our patient could not be calculated with certainty.

Parathyroidectomy can be total parathyroidectomy with auto transplantation or total parathyroidectomy.[9] The location of all parathyroid glands must be recognised during surgery, and particular attention must be paid to avoid injury to the inferior and superior thyroid arteries and RLNs. Superior parathyroid glands are located at the level of cricoid cartilage, 1cm above the intersection of the inferior thyroid artery and recurrent laryngeal nerve, while inferior parathyroid glands are located posterolateral to the lower pole of the thyroid gland, that is below the intersection of the inferior thyroid artery and recurrent laryngeal nerve. Surgery is more challenging in new-borns because of the limited surgical site, small parathyroid glands, and high risk of misinterpreting parathyroid glands with the lymph nodes. RLNs were identified and preserved during the procedure in the present case. This was confirmed by the presence of mobility of both vocal cords at the time of extubation and the absence of hoarseness of voice post-operatively.

Blood PTH level must be monitored during parathyroidectomy using intraoperative parathormone monitoring (IPM), the decision to continue exploration must be made accordingly. As the plasma half-life of PTH is 3-5 minutes, the blood PTH level must be monitored approximately 10 minutes after excision of the parathyroid glands, and the course of surgery must be planned accordingly. A significant decline in parathormone levels to the normal ranges implies that hyper-functioning parathyroid glands have been sufficiently removed. The surgical site must be re-explored if no significant decrease

occurs in parathormone levels and parathyroid glands in ectopic localisations must be explored. Total parathyroidectomy must be confirmed with frozen section and intraoperative parathyroid hormone levels. Both were not done in the present case due to their non-availability in our setup. However, complete excision was confirmed by postoperative parathyroid hormone levels and histopathology of parathyroid glands. If symptoms persist despite surgical intervention, missed parathyroid gland must be looked for at previous surgical site or ectopic locations.[9]

Histopathology in such cases usually shows chief cell hyperplasia of parathyroid glands. In the present case also, histology showed chief cells/clear cells hyperplasia.

Postoperatively, the patients need lifelong calcium and vitamin D supplementation to avoid hypocalcaemia.[10] The patient in the present case was put on calcium and Alpha Calcidiol supplementation.

Limitations: The QT interval or corrected QT interval could not be calculated on ECG.

Disclaimer: None to declare.

Conflict of Interest: The co-author is also head of the department and granted permission to publish this case report.

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