Original Article

Neonatal Severe Primary Hyperparathyroidism: A Series of Four Cases and their Long-term Management in India

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Abstract

Context: Neonatal severe primary hyperparathyroidism (NSPHPT) is an extremely rare autosomal recessive disorder, requiring a high index of suspicion. Infants affected with this disorder present with severe life-threatening hypercalcemia early in life, requiring adequate preoperative medical management followed by surgery. **Aims:** We report four newborns with NSPHPT who were managed over 10 years. **Subjects and Methods:** Demography, clinical presentation, treatment, and follow-up data were retrospectively studied with descriptive analysis to highlight the utility of long-term medical management, surgery, and genetic testing reported in the literature. **Statistical Analysis Used:** Descriptive Analysis. **Results:** We had three males and one female infant with a mean age of diagnosis at 28.7 days, calcium 29.2+/-2.8 mg/dL, and parathormone (PTH) 1963+/-270.4 pg/mL. All four infants presented with failure to thrive, hypotonia, and respiratory distress. All infants were treated medically followed by total parathyroidectomy plus transcervical thymectomy, with an additional hemithyroidectomy in one of them. Imaging was negative in all four cases. Three babies became hypocalcemic while the fourth infant had a drop in PTH and is on the tab. cinacalcet 30 mg/day. CaSR mutation was positive in three infants. **Conclusions:** Diagnosing NSPHPT needs expert clinical acumen. It requires emergency medical management to control calcium levels. The crisis may present later, necessitating parathyroidectomy in these cases once the child is fit for surgery. Surgery offers a cure for this unusual lethal hypercalcemia while the role of cinacalcet needs a special mention. Sound knowledge in endocrinology with parathyroid embryology and morphology is of paramount importance. Our case series might add a few insights into managing this unusual genetic disorder.

Keywords: Calcium-sensing receptor (CaSR), hypercalcemia, hypocalcemia, neonatal severe primary hyperparathyroidism (NSPHPT), parathyroidectomy

Introduction

Neonatal severe hyperparathyroidism (NSHPT) is an autosomal recessive disorder due to homozygous inactivating mutation of the calcium-sensing receptor (CaSR).[1] The calcium-set point is elevated leading to parathormone (PTH) secretion and renal absorption of calcium.[2] Hence, infants affected with this disorder present with very high PTH levels and severe hypercalcemia with a wide range of manifestations.[3] This condition is controlled with long-term medical treatment and can have an imminent crisis.[4,5] The cases reported have been accountable for sudden infant death syndromes with parathyroid hyperplasia, requiring parathyroidectomies to prevent fatal complications. We report our experience in the management and long-term follow-up of children with NSPHPT.

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Subjects and Methods

Four of our patients with NSHPT were managed in the last 10 years. All cases were managed by a team of endocrinologists, neonatologists, and a single endocrine surgeon. Retrospectively, demographic data, clinical presentation, treatment, and follow-up data were collected

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and descriptive analysis was performed. Informed consent and institutional ethical clearance were obtained.

Results

Case 1

An 80-day-old neonate presented with restlessness, sunken eyeballs, and dry mucosa on examination with normal vital parameters. [Tables 1 and 2] On evaluation, there was hypercalcemia, which was managed medically and calcium repeated at 1 month 6 days was 25.3 mg/dL. Blood urea nitrogen (BUN) and serum creatinine were normal -40 and 0.4 mg/dL (Normal: 6–20, 0.5–1.2 mg/dL). Serum parathormone measured by enzymatic chemiluminescent assay was 413.9 pg/mL and vitamin D was 11.2 (Insufficient: 10–30 ng/mL) [Tables 1, 3 and Figures 1, 2]. Postoperative fluctuating hypocalcemia was treated with intravenous calcium gluconate titrated according to the weight of the baby and calcitriol was replaced with oral drops with stabilization at the end of 1 week.

Case 2

Presentation and biochemical evaluation of the child revealed hypercalcemia [Tables 1-3]. Calcium repeated at 5 years of age was 14.5 mg/dL. The baby underwent surgery with postoperative serum calcium of 8.6 mg/dl while ionized calcium was 1.15 (Normal: 1.1-1.3mmol/l).

Case 3

This child was managed in an intensive care unit for 12 days. After medical management and stabilization, the child was taken up for surgery. Unfortunately, postoperative serum calcium dropped down to 12.2 mg/dL and PTH was 128 pg/mL, suggesting the leftover fourth gland. Reexploration was not attempted given the age and general condition of the child. The child is on cinacalcet 30 mg/day and is on frequent follow-up with no episodes of crisis.

Case 4

The 29-day-old male child was hypotonic with substernal chest retractions on examination. The mother underwent a cesarean section for oligohydramnios. The biochemical evaluation revealed hypercalcemia. Urine calcium was 32 mg/dL and urine creatinine was 7 mg/dL (normal <4.5). The calcium creatinine ratio was 1.87. The child was managed medically for 4 days. Peripheral X-rays showed severe osteopenia along with demineralization and osteolytic areas. The baby had a greenstick fracture of the left radius postoperatively, which was managed conservatively. A chest X-ray showed suspected right lung hemiagenesis. The child had a successful surgery with a histopathological and biochemical confirmation. The child had an episode of seizures followed by difficulty in breathing 1 week after surgery. He was put on mechanical ventilation and could not be weaned off, hence, he succumbed to death thereafter. Genetic testing was abandoned in this case.

The demographic profile of the 4 infants, brief summary, medical management, it's duration and surgical details were noted in Tables 1-3. Three males and one female had an unremarkable family history. Maternal and sibling calcium analysis was normal in all cases. USG and Sestamibi imaging was notably negative in all four cases. Three infants underwent total parathyroidectomy plus transcervical

Table 1: Demographic data and summary of 4 cases

Age at diagnosis	Sex	Presentation	S. Calcium (mg/dL)	Time of surgery (Days)	Follow-up
8 days	Male	Feeding problem, failure to thrive	25.3	48	Alive, normal calcium, not on medication
5 months	Male	Inappropriate milestones for age, URTI, hypotonia	19.3	1260	Alive, normal calcium, not on medication
1.5 months	Female	Hypotonia, failure to thrive	20.9	60	Alive, calcium- 11.4 mg/dL, on cinacalcet 10 mg/day
29 days	Male	Failure to thrive, hypotonia	19.6	35 days	Died, associated right lung hemiagenesis, Normal postop calcium

Table 2: Various parameters with means in all 4 cases

Parameters	Mean	1	2	3	4
S. Calcium (8.5-10.5 mg/dL)	29.2+/-2.8 (26-32)	30.3	19.9	20.9	19.6
S. Vit D (ng/mL)	11.5+/-2 (9-14)	11.2	11.9	13.5	13.9
PTH (1-65 pg/mL)	1382.6+/-1247.95 (135-2631)	413.9	196.5	2408	2512
S. Phosphorus (2.5-4.5 mg/dL)	2.48+/-0.25 (2.2-2.8)	2.4	2.2	2.5	2.8
SALK (20-140 IU/L)	1619+/- 809.07 (810-2428)	2248	432	1940	1856
Preop ICU stay (days)	8.1+/-3.2 (5-12)	5	8	12	6
Postop ICU stay (days)	14.2+/-16.8 (2-39)	9	2	15	38
No. of parathyroids removed	4 (3-5)	4	4+1	4+1	4+1
Follow-up period (months)	51.2 +/- 38.2 (2-84)	15	84	6	2
Postop Calcium (mg/dL)	6.7+/-2.2 (5.8-7.1)	9.2	8.6	12.4	9.6
Postop PTH (pg/mL)	34.8+/-62.3	10.2	<0.5	128	<0.5

thymectomy (PTx + TCT) while one infant underwent additional hemithyroidectomy.

Surgical procedure

Parathyroids were approached laterally after mobilizing the sternocleidomastoid on either side. They were identified in relation to the nerve, position of the superior being more consistent and posterolateral to the nerve. Inferior parathyroids are anteromedial to the nerve. Parathyroids are identified as pink structures with no surrounding fat, unlike the adults, where it is more yellow with surrounding fat. Some might be significantly enlarged; others being minimally enlarged owing to hyperplasia. All four parathyroids with the thymus were separated, carefully preserving the RLN's on both sides. The thymus is traced till the innominate vein ligated and removed to confirm the removal of supernumerary parathyroids if any. Postoperative drop in parathormone to negligible levels proves the completion of surgery. Further absolute evidence was provided by histopathological confirmation of parathyroids.

Three babies became hypocalcemic and are on calcium and vitamin D supplements with undetectable PTH levels. One infant's calcium and PTH dropped to 12.2 mg/dL and128 pg/mL, was maintained on calcimimetics.

Genetic testing

CaSR mutation was positive in three infants (a novel mutation in one).

The DNA extraction was done with a Qiagen kit from the whole blood EDTA. Sequencing was performed with

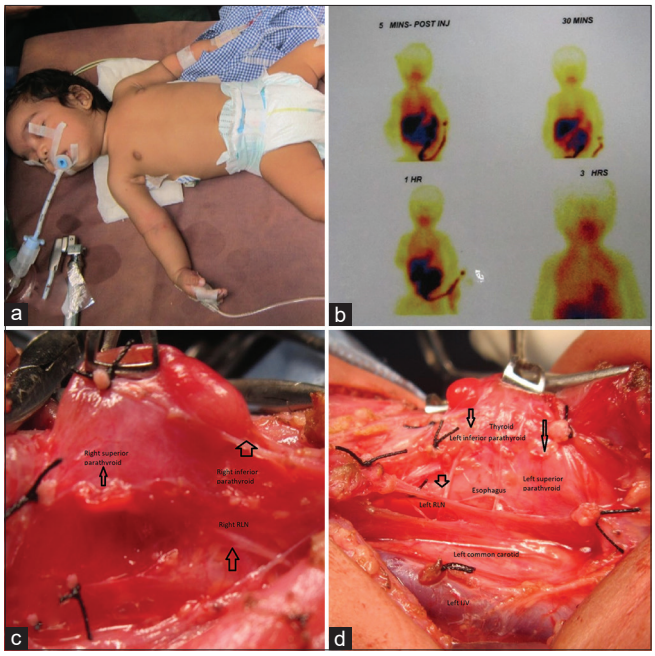

Figure 1: (a) preoperative 48 days old neonate, (b) intraoperative picture showing right sided parathyroids, (c) intraoperative picture showing left sided parathyroids, (d) Tc99 SESTAMIBI with no localization

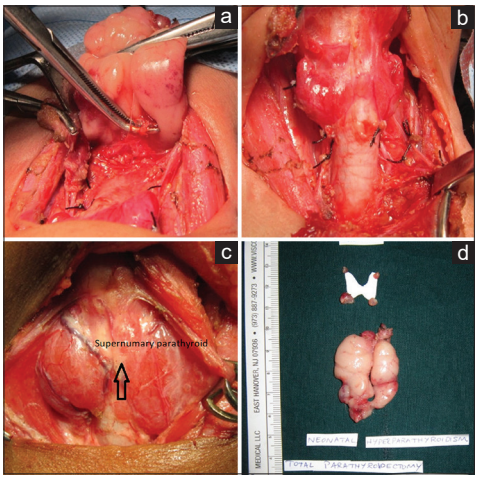

Figure 2: (a) transcervical thymectomy, (b) post excision surgical bed, (c) intraoperative picture showing supernumary parathyroid, (d) *in vitro* specimen

Table 3: Details of management of cases in our study

	Medical management	Surgery	Intraoperative findings	Histopathology	Genetic testing
Case 1	Hydration, saline diuresis, pamidronate, cinacalcet- 1 month	Total PTx + TCT	Bilaterally enlarged inferior parathyroids and mildly enlarged superior parathyroids.	4 parathyroids and no ectopia in the thymus	positive CaSR homozygous mutation
Case 2	Immediate saline diuresis, palmidronate and cinacalcet - 5 years.	Total PTx + TCT	Bilaterally enlarged inferior parathyroids, mildly enlarged superior parathyroids, few enlarged left level II lymph nodes, Supernumerary parathyroid was identified on the trachea just beneath the left RLN	5 parathyroids and no ectopia in the thymus	CaSR homozygous mutation
Case 3	Hydration, saline diuresis, cinacalcet- 12 days	Total PTx + TCT + Right hemithyroidectomy	Three parathyroids were identified with failure of identification of the fourth gland despite dissection of the paratracheal and carotid sheath, a nodule in the right lobe of the thyroid with the suspected intrathyroidal location of parathyroid	Three parathyroids in the specimen with the absence of any intrathyroidal parathyroid and normal thymus	CaSR homozygous mutation
Case 4	Immediate saline diuresis, palmidronate and cinacalcet for 4 days.	Total PTx + TCT	Bilaterally enlarged superior parathyroids and right inferior parathyroid, mildly enlarged left superior parathyroid, Suspected supernumerary parathyroid on the trachea	4 parathyroids and no ectopia in the thymus	Abandoned

dye terminators and fragments separated by capillary electrophoresis (ABI Prism 3130). Seven exons coding the calcium-sensing receptor were sequenced, homozygous c2319delG, c2244G>C novel mutations were noted in the sixth exon. Targeted gene sequencing was done in the third case with a homozygous novel variant, c492 + 1G >C mutation noted in the 5' splice site of the third intron.

Our observations: NSPHPT differs from the adult variety of PHPT in being more clinically severe, most often precipitating a crisis. Neonates usually do not present with the classical manifestations of PHPT in adults like pain abdomen, bony abnormalities, renal stones, etc. Infants in our study mainly presented with failure to thrive, life-threatening dyspnea requiring emergency admissions. Two of them did have classical osteopenia. Due to multiglandular involvement, imaging is not helpful in these cases. Genetic mutations are classical in these cases unlike the routine PHPT's. Lastly, the postoperative fall in the calcium levels is more gradual in these cases, probably due to the prolonged hypercalcemia in contrary to the adult cases with the classical fall in calcium within 24 h of surgery. These were our novel observations in the series, which would contribute to adding insights to further management and study in this direction.

Discussion

NSHPT is a very rare inherited disorder associated with inactivating mutations in calcium-sensing receptors (CaSR) genes located in chromosome 3p-13.3-21 loci.[1] Hyperparathyroidism is a rare disease in children compared to adults. Primary hyperparathyroidism due to a single parathyroid adenoma is the commonest cause in both adults and children.[1,6] In neonates, hyperparathyroidism can be due to transient neonatal hyperparathyroidism as a consequence of maternal hypocalcemia. Our series had four neonates presenting at a mean of 28 days duration compared to a 2-week interval in the other two series.[2,7-9] Homozygous loss of function mutations leads to NSHPT characterized by severe hyperparathyroidism early in the first week of life with severe metabolic bone disease and life-threatening hypercalcemia (>20 mg/dL). Our series had presentations including failure to thrive, hypotonia, skeletal demineralization, respiratory distress just like the other series.[3-9] Our series had an average serum calcium of 29.3 mg/dL. In NSHPT, the complete absence of CaSR in parathyroids leads to hyperplasia of all the four glands. Hence, there is no role for preoperative localization studies. Imaging was negative in our series, reiterating the futile preoperative localization.[4-9]

All four of our cases required management of the crisis with saline diuresis and medical management including bisphosphonates and cinacalcet. One of the babies was maintained on cinacalcet for 5 years before undergoing surgery. Neonates can present with a hypercalcemic crisis which should be managed before the proposed parathyroidectomy. Initial management includes adequate intravenous fluids to correct dehydration, once the intravascular volume is restored loop diuretics are added to prevent fluid overload and to inhibit calcium reabsorption in the kidney. Hemodialysis may be required in children with renal failure. No babies required dialysis in our study. Bisphosphonates and cinacalcet can serve as rescue therapy when urgent surgery cannot be performed.[5] Bisphosphonate inhibits osteoclast-mediated bone resorption. Preoperative administration of pamidronate to control severe hypercalcemia has been reported by Waller and Al-shafaney *et al*.[6,8] CaSR is a G-protein receptor located in parathyroid glands and kidney, which plays an important role in calcium homeostasis. Heterozygous loss of function mutation leads to familial hypocalciuric hypercalcemia (FHH), a milder form of the disease which is usually asymptomatic. Novel homozygous mutations were found in three of our cases as reported in other series. Earlier, it was believed that these cases of hypercalcemia are medically treatable, with the advent of new drugs. Calcimimetics act as allosteric activators of CaSR, binding to the transmembrane region, thus increasing receptor sensitivity to calcium. Savas Erdeve *et al.* reported that one of their cases with a particular novel mutation could be treated with cinacalcet (25 g/m2/day), suggesting that the location of the mutation on the transmembrane receptor and the residual function of CaSR protein determines the success of calcimimetic treatment. Persistent hypercalcemia despite prolonged treatment with drugs and remarkable improvement in the quality of life and fall in serum calcium levels propagated surgery as the way of eventual management.[7-9]

Medical management will only control the calcium levels, which may exacerbate the hypercalcemia eventually leading to the crisis.

The key to the absolute cure of hypercalcemia remains surgery. All four babies underwent total parathyroidectomy and transcervical thymectomy in our series with the addition of hemithyroidectomy in one case, with the suspicion of intrathyroidal parathyroid. Surgical removal of abnormal glands remains the definitive treatment, which was first introduced in 1964. Surgery in neonates is quite challenging owing to the difficulty in parathyroid gland identification, requiring sufficient expertise. Parathyroid autotransplant was avoided in all cases owing to extremely high recurrence rates as shown in the literature[4-8] and the good compliance of patients requiring permanent calcium supplements. Earlier, subtotal parathyroidectomy was performed which has high recurrence rates. Nowadays, total parathyroidectomy with or without autotransplantation is increasingly being performed in most centers. Autotransplantation can lead to graft dependent hypercalcemia in 33% and a failure rate of 6%.[7-11] Hence, most of the surgeons now prefer total parathyroidectomy without autotransplantation. Al Shafaney *et al*., reported no recurrence following autotransplantation in his series of five patients.[8] Savas-Erdeve *et al.* have reported one case of recurrence following autotransplantation which required removal after 124 days of age.[9] S. Alagaratnam *et al.* reported a series of five cases as mentioned in Table 4. Although biochemical cure

Table 4: Comparison of our series with other three published series

Parameters/Comparison	Our study	Saud Al-Shanafey *et al*.[8]	Savas-Erdeve *et al*.[9]	S. Alagaratnam *et al*.[10]
Number	4	5	2	6
Study period (years)	10	10	-	34
Gender M: F	3:1	2:3	1:1	3:3
Age at diagnosis	15-60 days (Mean 28.7 +/-21.3 days)	7 to 30 days (mean 18 days)	-	3 to 120 days (median 2 weeks)
Calcium level	22.4 mg/dL	3.84 mmol/L (mean)	18.3 mg/dL (mean)	3.03-8.10 mmol/L (median 4.02)
PTH level	1963 pg/mL	3607 ng/L (mean)	2433 pg/mL (mean)	15.8-360 pmol/L (median 56.9)
Total parathyroidectomy	4+ thymectomy	5	2	5
Subtotal parathyroidectomy	-	-	-	1

was not attained, the patient was asymptomatic and managed conservatively.[10]

Because of the rarity of the disease, only a few case series including ours were reported in the literature till date [illustrated in Table 4].[8-10]

Postoperative hypocalcemia is common following total thyroidectomy without autotransplantation, which can be managed with oral calcium and calcitriol supplementation. Nephrocalcinosis due to chronic calcitriol supplementation is not seen in patients with NSHPT because of decreased renal CaSR function.[12-15]

A few case reports by Kulkarni and Al-Shaikh *et al.* showed that the neonates presented in the first month of life, one treated medically and the other maintained on medical management after failed surgery, suggesting a role for prolonged medical management.[16,17]

Conclusion

NSPHPT is an extremely uncommon diagnosis that needs a very high index of suspicion in neonates and proves a challenge to any clinician specializing in endocrinology. NSPHPT presents with life-threatening calcium levels which can be managed with long-term medical management to adequately prepare the patient for surgery, ultimately curing the disease. Overall management requires a good multidisciplinary team consisting of an endocrinologist, endocrine surgeon, and nuclear physician, contributing to the right diagnosis and management plan. The key to successful surgery is to identify four parathyroids including ectopic and supernumerary glands. These children need lifelong calcium and vitamin D supplementation which requires adequate counseling and compliance.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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