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CLINICAL BRIEF

A Case of Neonatal Severe Hyperparathyroidism: Challenges in Management

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Abstract
Neonatal severe hyperparathyroidism is a rare disorder arising from inherited defects in the calcium sensing receptor (CaSR) that presents early in life with severe hypercalcemia, failure to thrive, and developmental retardation. The authors describe an infant with neonatal severe hyperparathyroidism due to homozygous *CaSR* gene mutation presenting with recurrent episodes of severe hypercalcemia, growth retardation, and developmental delay. Medical management served as an effective bridge therapy to surgery. Total parathyroidectomy with right hemithyroidectomy was performed at 7 mo of age and resulted in successful cure and normalization of growth and developmental milestones. Timely medical and surgical management can help prevent mortality and morbidity in the form of neurodevelopmental sequelae. Life-long monitoring and treatment is mandatory for the resultant hypoparathyroidism.

Keywords Calcium sensing receptor (CaSR) · Hypercalcemia · Total parathyroidectomy

Introduction

Neonatal severe hyperparathyroidism (NSHP) is a rare life-threatening disorder presenting with hypercalcemic crisis in the first week of life. It is an autosomal recessive disorder caused due to inactivating homozygous or compound heterozygous mutation in calcium sensing receptor (*CaSR*) gene (chromosome 3p-13.3-21). Medical management using bisphosphonates and calcimimetic drugs has been tried with variable outcomes and total parathyroidectomy is invariably required in most cases [1, 2]. Delayed treatment can lead to neurological deficit and developmental delay.

Here, the authors report a child with NSHP with severe hypercalcemia, global developmental delay (GDD), and failure to thrive (FTT), and the medical and surgical management of NSHP.

Case Report

A 20-d-old girl (first born to 3rd degree consanguineous couple by normal delivery and birth weight 3.1 kg) was symptomatic since day 3 of life with lethargy, refusal to feed, constipation, and weight loss. On examination, vitals were stable, weight was 2.7 kg, and she was dehydrated, lethargic, and hypotonic. Investigations are summarized in Table 1. Hypercalcemia was managed with hyperhydration (1.5 times maintenance fluid) and furosemide (1 mg/kg) for 4–5 d, after which, calcium levels decreased drastically (14 mg/dL) and she was discharged on oral cinacalcet—a calcimimetic agent (30 mg/d).

Her father had mild hypercalcemia (10.8 mg/dL) with low fractional excretion of calcium suggestive of familial hypocalciuric hypercalcemia. Screening of other family members was unremarkable. Exome sequencing revealed homozygous

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Table 1 Clinical and laboratory parameters at diagnosis, surgery, and follow-up

	Normal range	2 wk of age (1st admission)	4 mo of age (2nd admission)	6 mo of age (3rd admission)	7 mo of age (4th admission)	14 mo of age (postsurgery follow-up)
Ca (mg/dL)	8.6–10.8	36.9	24	27.6	13.2	10.3
P (mg/dL)	4.8–7.4	3.6	2.3	3.5	3.1	7.1
ALP (U/L)	30–141	445	468	512	417	162
iPTH (pg/mL)	12–88	529	NA	NA	636.5	1.8
25-OH-Vit D (ng/mL)	> 30	13.0	NA	NA	5.6	132
Urine Ca/Creatinine ratio	< 0.2	1.08	0.17	NA	0.11	NA
Developmental age		NA	NA	NA	GM: 2–3 mo FM: 5–6 mo Social and language: 4–5 mo	GM: 11 mo FM: 15 mo Language: 10 mo Social: 1 y
Weight (kg)		2.75 kg	NA	4.5 kg	5.46 kg (−3.1 SD)	8 kg (−1.3 SD)
Length (cm)		NA	NA	NA	62 cm (−2.8 SD)	74 cm (−0.9 SD)
Head circumference (cm)		NA	NA	NA	40 cm (−2.5 SD)	46 cm (0.3 SD)
Weight for length		NA	NA	NA	−1.7 SD	−1.2 SD

25-OH-Vit D 25-hydroxy vitamin D, *ALP* Alkaline phosphatase, C*a* Calcium, *FM* Fine motor, *GM* Gross motor, *iPTH* Intact parathyroid hormone

frameshift mutation in *CaSR* gene (c.2364delC; p.Tyr789fs in exon 7) confirming the diagnosis of NSHP. Total parathyroidectomy was delayed due to COVID-19 pandemic. She was readmitted with hypercalcaemic crisis at 3 and 6 mo of age (Table 1). Bisphosphonate was given in both the admissions (zoledronic acid 0.025 mg/kg). Her calcium levels improved transiently but she continued to have FTT, intermittent constipation, and GDD. Subsequently, she was referred at 7 mo of age for surgical intervention.

At 7 mo, she was underweight, stunted, and hypotonic. Her urine calcium-to-creatinine ratio was normal (0.11) with no nephrocalcinosis. Skeletal survey showed diffuse osteopenia with no lytic lesions. Sestamibi scan did not show any uptake. 4D CT revealed small lesion in the right inferior parathyroid gland, possibly hyperplasia.

Following failure of medical management, total parathyroidectomy was done with autotransplantation of a part of right superior parathyroid gland in right brachioradialis. Intraoperative iPTH levels at 10 and 15 min of resection were 154.9 and 153 pg/mL, respectively. On postoperative day 3, iPTH level was 66 pg/mL and serum calcium was 8.5 mg/dL. However, her calcium and iPTH levels again started rising to 12.6 mg/dL and 116 pg/mL, respectively by postoperative day 6. Histopathology report showed 3 parathyroid glands; however, the right inferior parathyroid specimen showed only thymic tissue. In view of recurrence of hypercalcemia and elevated iPTH, re-exploration was done; however, right inferior parathyroid gland could not be localized. Few enlarged nodules were visualized on right side of thyroid gland inferiorly and were found to be fibrofatty tissue on frozen section. Serum iPTH levels at 10 and 15 min of resection were 53 and 63 pg/mL, respectively. Subsequently, right hemithyroidectomy was done, after which, iPTH levels decreased to 7.92 pg/mL. Child was discharged on oral calcium, vitamin D3, and 1, 25 hydroxy vitamin D in view of postoperative hypocalcemia (7.5 mg/dL). On follow-up, child had significant improvement in growth and developmental milestones (Table 1).

Discussion

Acute management of NSHP involves hyperhydration, loop diuretics, calcitonin, and bisphosphonates to decrease calcium levels acutely [3–5]. Cinacalcet is an allosteric activator of CaSR and has been used for acute and long-term management with variable results. To date, 9 cases of NSHP (5-heterozygous, 1-compound heterozygous and 3-homozygous mutation) have been successfully treated with cinacalcet. Literature on long-term safety of bisphosphonates and cinacalcet in children is lacking [1, 5].

Total parathyroidectomy with or without autotransplantation of parathyroid gland is the definitive therapy for children who fail medical therapy [3, 4]. It is often challenging in newborns due to limited surgical field and small-sized glands. Preoperative localization of parathyroid gland using MRI, CECT neck, sestamibi scan, or contrast USG is often attempted but is rarely of any help [6]. Monitoring of

intraoperative PTH levels is useful; as PTH has short half-life, results are available within 10–20 min and rapid decline in levels suggest successful removal of all parathyroid tissue [7]. Failure of PTH levels to return to normal range suggests incomplete parathyroidectomy or presence of ectopic gland which may be located in thymus, intrathyroidal area, posterior mediastinum, or retropharyngeal area [6, 8].

In the present case, medical management decreased calcium levels acutely but failed as a long-term measure. The child also required re-exploration and hemithyroidectomy due to presence of ectopic tissue in the thyroid gland. She continued to require calcium and vitamin D supplementation even after 6 mo of surgery suggesting autograft failure.

Conclusion

Medical management is important to tide over acute hypercalcemic crisis in NSHP; however, surgical management is the definitive therapy with benefits in growth and development. Lifelong monitoring and treatment of resultant hypoparathyroidism is mandatory to avoid hypocalcemia and its complications.

Authors' Contributions PG was involved in patient care, collecting the data, and drafting the manuscript; SAT, AVS, RAM, VJ helped with clinical care and provided inputs to the paper; SA performed surgery on the patient and provided inputs to the paper; RS was involved in patient care, critically revised and finalized the manuscript; All authors have accepted the responsibility for the entire content and approved the final manuscript for submission. RS will act as the guarantor for this paper.

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Data Availability Yes.

Declarations

Conflict of Interest None.

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