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NEONATAL HYPERCALCEMIA: A COMPREHENSIVE REVIEW WITH THREE INSTRUCTIVE CASE STUDIES

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ABSTRACT **Background:** Neonatal hypercalcemia is rare but can cause serious complications, including dehydration, arrhythmias, neurological depression, and nephrocalcinosis. Early etiologic classification is essential for effective management. **Objective:** To present three challenging neonatal hypercalcemia cases—two due to neonatal severe hyperparathyroidism (NSHPT) and one due to subcutaneous fat necrosis (SCFN)—and to summarize diagnostic and therapeutic considerations. **Methods:** A descriptive case series was analysed for clinical features, laboratory profile, imaging, management, and outcomes. A focused literature review was performed to contextualize findings. **Results:** Two infants exhibited profound hypercalcemia and markedly elevated PTH levels confirming NSHPT. Despite hydration, bisphosphonates, and cinacalcet, calcium control was transient, and both infants died without definitive parathyroidectomy. The third infant had SCFN following perinatal asphyxia; hypercalcemia improved with hydration and corticosteroids and did not recur. **Conclusion:** Rapid, PTH-guided evaluation is vital in neonatal hypercalcemia. NSHPT requires early surgical intervention, whereas SCFN typically responds to medical therapy but warrants close monitoring.

KEYWORDS : Neonatal Hypercalcemia, Neonatal Severe Hyperparathyroidism, Neonatal Subcutaneous Fat Necrosis.

INTRODUCTION

Calcium homeostasis in the neonatal period is delicately balanced through coordinated regulation by PTH, vitamin D metabolites, calcium-sensing receptors (CaSR), and renal and skeletal responses. Hypercalcemia in neonates is far less common than hypocalcemia but carries more significant consequences due to its potential for irreversible renal injury, particularly nephrocalcinosis and tubular dysfunction. Early identification is challenging because symptoms are non-specific and easily attributed to common neonatal issues.

Hypercalcemia is defined as an ionized calcium concentration above 1.35 mmol/L (5.4 mg/dL) or total serum calcium above 2.7 mmol/L (10.8 mg/dL) [1]. Understanding the underlying etiology is essential because management varies widely—from simple hydration to parathyroidectomy.

In this study, we present three illustrative cases of neonatal hypercalcemia representing two major etiological groups:

1. PTH-dependent hypercalcemia (two cases of NSHPT), and
2. PTH-independent hypercalcemia (SCFN).

We highlight diagnostic challenges, clinical deterioration despite standard therapies, and reasons behind treatment failures. Alongside these cases, a detailed review of etiologies and modern management principles is presented.

Case Presentations:

Case 1: Neonatal Severe Hyperparathyroidism with Fulminant Course

A 25-day-old male infant presented with lethargy, poor feeding, tachypnea (68/min), bradycardia (90/min), and significant hypotonia. Born to consanguineous parents, he had no perinatal complications. Initial laboratory evaluation revealed profoundly elevated serum calcium (29 mg/dL), markedly increased PTH levels, and vitamin D deficiency. Importantly, both parents had mildly elevated calcium levels, suggesting an autosomal pattern of CaSR dysfunction.

Imaging—including Ga-68 DOTANOC PET and 99mTc-sestamibi scans—did not localize ectopic or enlarged parathyroid tissue. Standard therapies such as hyperhydration and IV bisphosphonates failed to normalize calcium. Subsequent initiation of the calcimimetic cinacalcet led to partial biochemical improvement.

Despite counselling regarding the necessity of parathyroid exploration and genetic analysis, parents opted to discontinue treatment. The infant died one month later, likely due to complications of recurrent severe hypercalcemia.

Case 2: Recurrent Hypercalcemia and Respiratory Distress due to NSHPT

A 2-month-old male presented with failure to thrive and worsening respiratory distress. Hypercalcemia had been first detected at 17 days of life (Ca- 28.4 mg/dL). Initial improvement was achieved with saline diuresis, short-course oral steroids, and IV pamidronate; however, hypercalcemia recurred.

On referral to our centre, he had pallor, mild proptosis, and hypotonia. Both MIBI imaging and Ga-68 DOTANOC PET failed to localize hyperfunctioning parathyroid tissue. Extremely elevated PTH levels combined with hypercalcemia confirmed NSHPT. Treatment with IV pamidronate and cinacalcet normalized calcium levels temporarily.

Despite extensive counselling regarding surgical cure, the family declined definitive parathyroidectomy. The infant died about one month after discharge, likely from another episode of life-threatening hypercalcemia.

Case 3: Subcutaneous Fat Necrosis of the Newborn with Hypercalcemia

A 15-day-old male infant was referred with hypercalcemia (18.5 mg/dL) and multiple erythematous, firm swellings over the cheeks, back, and limbs. Perinatal history included significant asphyxia and maternal preeclampsia. Imaging revealed fat-rich lesions consistent with SCFN.

Despite adequate hydration and brief IV hydrocortisone therapy, calcium remained elevated; oral prednisolone was added, leading to gradual normalization. The infant has since remained clinically stable, without rebound hypercalcemia.

This case illustrates the classic but often under-recognized pathway of PTH-independent hypercalcemia due to granulomatous overproduction of 1,25-dihydroxyvitamin D in SCFN. Below Table 1 shows the details of biochemical reports of all cases.

Table 1: Biochemical Reports of 3 cases.

Biochemical parameters	Case 1	Case 2	Case 3
Serum vitamin D (ng/ml) (normal: 25-80)	8.6	13.2	35.9
Serum PTH (pg/ml) (normal: 10-80)	11451	977	0.8
Serum Magnesium (mg/dl) (normal: 1.7-2.2)	2.1	2.76	2.3
Spot urine calcium: creatinine ratio (normal: <0.2)	9.77	4.56	5.18
Infantogram	No fracture	No fracture	No fracture
USG abdomen	Nephro-calcinosis +	Nephro-calcinosis+	Nephro-calcinosis+

Special tests	Mother's: Ca-11.3mg/dl, PO4-4.1mg/dl, ALP-165.7U/L. Father's: Ca-11mg/dl, PO4-3.8mg/dl, ALP-185.4U/L	Mother's: Ca-9.9 mg/dl, PO4- 2.9 mg/dl, ALP-102.3 U/L Father's: Ca-9.9 mg/dl, PO4- 3.8 mg/dl, ALP-117.6 U/L	Serum Triglyceride - 349 mg/dl Mother's Triglyceride - 123mg/dl Father's Triglyceride - 110mg/dl

DISCUSSION

Table 2: shows the Aetiologies of Neonatal Hypercalcemia.

PTH Dependent Hypercalcemia	PTH Independent Hypercalcemia
• Neonatal Severe Hyperparathyroidism (NSHPT): Caused by homozygous or compound heterozygous CaSR gene mutations. Presents with extreme hypercalcemia, respiratory distress, fractures, hypotonia, and failure to thrive. • Primary Hyperparathyroidism: Rare solitary adenoma. • Secondary Hyperparathyroidism: Maternal vitamin D deficiency or maternal hypoparathyroidism causing fetal parathyroid hyperplasia. • Familial Hypocalciuric Hypercalcemia (FHH): Typically benign; heterozygous CaSR mutation.	• Iatrogenic: Excess calcium salts or vitamin D overdose; low-phosphate formulas. • Vitamin D–related: o Intoxication o CYP24A1 mutation (Idiopathic Infantile Hypercalcemia) o SCFN (granulomatous conversion of vitamin D) • Genetic syndromes: Williams syndrome. • Endocrine disorders: Hyperthyroidism or calcitonin deficiency. • Tumour-mediated: PTHrP producing tumors (rare in neonates). • Inborn errors of metabolism: Hypophosphatasia, Blue diaper syndrome.

Table 3: Shows Investigations Required

Blood:

Total and ionized calcium, pH, phosphorus, alkaline phosphatase, creatinine, serum albumin, intact PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, Thyroid function test

Urine:

Calcium/creatinine ratio, tubular reabsorption of phosphate

Renal ultrasonography

Special tests if needed:

PTH Related protein

Vitamin A

Parents' serum calcium and urine calcium

Management Strategies

Therapeutic goals include reducing serum calcium, promoting renal excretion, inhibiting bone resorption, and addressing the underlying cause.

Hydration and Diuresis: First-line for all significant hypercalcemia:
- Normal saline (150–200 mL/kg/day)
- Furosemide (0.5–1 mg/kg every 6 hours) after hydration

Bisphosphonates: Potent inhibitors of osteoclastic bone resorption.
Pamidronate Dose: 1 mg/kg/day.
Effective in both NSHPT and SCFN-associated hypercalcemia.
Calcimimetics (Cinacalcet): Enhance CaSR sensitivity, suppressing PTH secretion.
Dose: 0.4–9.6 mg/kg/day.
Success depends on mutation type and residual CaSR function.
Glucocorticoids: Reduce 1α-hydroxylase activity and intestinal calcium absorption.
Useful in SCFN and vitamin D intoxication.
Calcitonin: Short-acting inhibitor of osteoclasts.
Provides rapid but temporary reduction in calcium.
Dialysis: Indicated for refractory or life-threatening hypercalcemia.
Surgery: Definitive therapy for NSHPT.
Options includes subtotal or total parathyroidectomy with auto-transplantation.
Intraoperative PTH monitoring improves surgical success.

NSHPT: A Race Against Time

NSHPT is the most severe form of neonatal hypercalcemia. Without surgical intervention, mortality is high, as illustrated by our two cases. Although calcimimetics and bisphosphonates offer temporary relief, they rarely provide long-term control in cases with complete CaSR loss of function.

Mutation type determines responsiveness to cinacalcet. Mutations within the transmembrane region often impair drug binding, leading to treatment failure. In India first newborn with NSHPT managed by total parathyroidectomy was reported by Aggarwal et al [2]. Wilhelm-Bals et al [3]reported even after parathyroidectomy, IV bisphosphonate and Cinacalcet were used to reduce persistent hypercalcemia. Similarly in few studies pharmacological drugs have shown to have good result [4,5]. Long term neurological follow up in medically treated patients were as good enough as surgically operated patients [3,6]

SCFN: Benign but not Harmless

SCFN is typically self-limiting, yet the hypercalcemia it causes can be severe and prolonged. The granulomatous tissue expresses excess 1α-hydroxylase, producing high levels of active vitamin D. 51% of reported SCFN cases had hypercalcemia [7]. Hypercalcemia can be a serious complication and should be treated as early as possible or else calcification within the swelling [8] or metastatic calcification [9,10] can occur. Hypercalcemia can persist for many year [10]. Hypercalcaemia developing 6 months after the skin manifestations is also reported [11]. Treatment options for hypercalcemia due to SCFN as stated by studies includes: wait and watch in case of asymptomatic mild hypercalcemia, hydration and diuresis therapy [12], glucocorticosteroids- oral Prednisolone [9] and IV Methylprednisolone [13], IV Pamidronate [14], depending on the severity of hypercalcemia level and symptoms.

CONCLUSION

Neonatal hypercalcemia is a complex clinical condition with widely varied etiologies and outcomes. Early recognition, structured diagnostic evaluation, and targeted management are essential to prevent permanent renal damage and mortality.

NSHPT demands urgent surgical intervention, especially when pharmacotherapy provides only transient improvement. SCFN, while often benign, requires vigilant monitoring due to risk of delayed or prolonged hypercalcemia.

A systematic, PTH-guided approach remains the cornerstone of effective diagnosis and treatment.

REFERENCES

1. Rodd C, Goodyer P. (1999), Hypercalcemia of the newborn: etiology, evaluation, and management (1999) Pediatr Nephrol 6:542-547.
2. Aggarwal, V., Sahni, M., Gupta, N., & Khandelwal, D. (2017). A challenging case of neonatal hyperparathyroidism. Thyroid Research and Practice, 14, 130–132.
3. Wilhelm-Bals, A., Parvex, P., Magdelaine, C., & Girardin, E. (2012). Successful use of bisphosphonate and calcimimetic in neonatal severe primary hyperparathyroidism. Pediatrics, 129(3), e812–e816.
4. Gannon, A. W., Monk, H. M., & Levine, M. A. (2014). Cinacalcet monotherapy in neonatal severe hyperparathyroidism: A case study and review. Journal of Clinical Endocrinology & Metabolism, 99, 7–11.
5. Fisher, M. M., Cabrera, S. M., & Imel, E. A. (2015). Successful treatment of neonatal severe hyperparathyroidism with cinacalcet in two patients. Endocrinology, Diabetes & Metabolism Case Reports, 2015(1).
6. Janik, E., Bloch, C. A., & Janik, J. S. (2000). Intrathyroid parathyroid gland and neonatal primary hyperparathyroidism. Journal of Pediatric Surgery, 35(10), 1517–1519.
7. Stefanko, N. S., & Drolet, B. A. (2019). Subcutaneous fat necrosis of the newborn and associated hypercalcemia: A systematic review of the literature. Pediatric Dermatology, 36(1), 24–30.
8. Beuzeboc, G. M., Aillet, S., Bertheuil, N., Delliere, V., Thienot, S., & Watier, E. (2014). Surgical management of subcutaneous fat necrosis of the newborn required due to a lack of improvement: A very rare case. British Journal of Dermatology, 171(1), 183–185..
9. Dudink, J., Walther, F. J., & Beekman, R. P. (2003). Subcutaneous fat necrosis of the newborn: Hypercalcaemia with hepatic and atrial myocardial calcification. Archives of Disease in Childhood – Fetal and Neonatal Edition, 88(4), F343–F345.
10. Lara, L. G., Villa, A. V., Rivas, M. M., Capella, M. S., Prada, F., & Enseñat, M. A. (2017). Subcutaneous fat necrosis of the newborn: Report of five cases. Pediatrics & Neonatology, 58(1), 85–88.
11. Mahé, E., Girszyn, N., Hadj-Rabia, S., Bodemer, C., Hamel-Teillac, D., & De Prost, Y. (2007). Subcutaneous fat necrosis of the newborn: A systematic evaluation of risk factors, clinical manifestations, complications and outcome of 16 children. British Journal of Dermatology, 156(4), 709–715.

12. Mitra, S., Dove, J., & Somisetty, S. K. (2011). Subcutaneous fat necrosis in newborn—An unusual case and review of the literature. European Journal of Pediatrics, 170(9), 1107–1110.
13. Chrysaidou, K., Sargiotis, G., Karava, V., Liasis, D., Gourvas, V., Moutsanas, V., Christoforidis, A., & Stabouli, S. (2021). Subcutaneous fat necrosis and hypercalcemia with nephrocalcinosis in infancy: Case report and review of the literature. Children, 8(5), 374.
14. Lombardi, G., Cabano, R., Bollani, L., Del Forno, C., & Stronati, M. (2009). Effectiveness of pamidronate in severe neonatal hypercalcemia caused by subcutaneous fat necrosis: A case report. European Journal of Pediatrics, 168(5), 625–627.