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Case Reports

A Rare Cause of Symptomatic Neonatal Hypocalcaemia

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Abstract Neonatal hypocalcaemia due to maternal hyperparathyroidism is a well-known but relatively rare condition. A 10-day-old infant presented with neonatal convulsion was found to have hypocalcaemia, hypomagnesium, hyperphosphataemia and inappropriately low parathyroid hormone level. Investigation of the asymptomatic mother showed hypercalcaemia due to parathyroid adenoma. Evaluations of both neonatal and maternal parathyroid status are indicated in investigation of neonatal hypocalcaemia.

Key words Hyperparathyroidism; Neonatal hypocalcaemia; Seizures

Case Report

A 10-day-old male infant was admitted via Accident and Emergency (A&E) Department because of repeated episodes of facial and limbs twitching for 1 day. He was the second child of a 29-year-old lady with good past health. The baby was delivered by vacuum extraction at term (Birth weight: 3.235 kg) in a private hospital and was subsequently discharged on Day 4. He was fed with breast milk and formula milk in the first few days of life and full formula milk feeding was just commenced on the day before onset of symptoms.

The infant was found to have left-sided facial twitching since Day 9 of age. When the baby was admitted to our unit on Day 10, repeated episodes of eye blinking, facial and four limbs twitching, cyanosis and loss of consciousness were noted. Each convulsive episode lasted for about 30 to 60 seconds. Intravenous diazepam and midazolam were given to abort the seizures.

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Physical examination revealed a well, alert and afebrile infant with normal vital signs. No dysmorphism and no focal neurological deficit were noted. Examination of other systems showed no abnormality and there was no clinical evidence of DiGeorge syndrome.

Initial laboratory evaluation showed significant hypocalcaemia (Total calcium: 1.21 mmol/l and ionised calcium: 0.6 mmol/l). Blood glucose and other electrolytes were normal. Intravenous calcium replacement was given in form of 10% calcium gluconate followed by maintenance intravenous fluid with calcium supplement. The infant was then transferred to our neonatal intensive care unit (NICU) for further management.

After admission to NICU, he had another episode of cycling movement of lower limbs, upper limbs twitching, loss of consciousness and eye staring. This was aborted by intravenous midazolam and phenobarbitone was then loaded for seizure control.

Total calcium (1.39 mmol/l; normal range 2.20-2.60 mmol/l) and ionised calcium levels (0.75 mmol/l; normal range 0.98-1.21 mmol/l) were still low on admission to NICU. There were also hyperphosphataemia (3.47 mmol/l; normal range 0.80-1.40 mmol/l) and hypomagnesaemia (0.54 mmol/l; normal range 0.70-1.10 mmol/l). Serum concentration of parathyroid hormone (PTH) was inappropriately low (1.19 pmol/l; normal range 1.20-5.70 pmol/l) despite low calcium level. There was no biochemical evidence of rickets.

Calcium infusion was given as initial therapy. The infant

had no more seizure when ionised calcium level reached low normal range on the next day. Phenobarbitone and intravenous calcium supplement were then stopped. Formula feeding (Nan I) was commenced and oral calcium was given in form of calcium gluconate 600 mg four times daily (Elemental calcium ~65 mg/kg/day) until Day 21 when ionised calcium level had stabilised. Magnesium salt was also given in form of oral magnesium sulphate ($MgSO_4$) 400 mg four times daily for hypomagnesium. Vitamin D_2 (ergocalciferol) at 400 IU per day was given from Day 13 to Day 80. The infant was finally discharged on Day 26 and was followed regularly for progress. Parathyroid hormone level rechecked on Day 49 lied within the normal range (3.29 pmol/l). Phosphate level slowly returned to normal at three months of age (1.91 mmol/l). He was clinically well and thriving with no further convulsion after discharge.

Maternal blood investigation revealed high calcium (2.64 to 2.98 mmol/l), low phosphate (0.6-0.91 mmol/l) and high serum parathyroid hormone level (14.99 pmol/l). These findings were all compatible with the diagnosis of neonatal hypocalcaemia due to maternal hyperparathyroidism. She was then referred to the medical unit for further investigation and a right parathyroid adenoma was subsequently found and removed surgically.

Discussion

In utero, there is an active placental transport of calcium from mother to foetus resulting in higher foetal calcium level than maternal value. This relative hypercalcaemia will suppress the foetal parathyroid hormone secretion. At birth, cessation of maternal calcium transfer and the hypoparathyroid state will lead to transient asymptomatic hypocalcaemia in early neonatal life. This relative hypocalcaemic state will then stimulate parathyroid hormone secretion and suppress calcitonin production. Calcium level usually normalizes by 5 to 10 days of life, unless this physiological transition of calcium metabolism is altered by other clinical conditions.

There are two peaks in the occurrence of neonatal hypocalcaemia (Table 1). Early-onset neonatal hypocalcaemia is commonly seen in infants with prematurity and low birth weight or due to complications in pregnancy (e.g. maternal insulin-dependent diabetes) and delivery (e.g. birth asphyxia) but the etiology is usually multifactorial (Table 2). This condition typically occurs during the first few days of life, with the lowest calcium concentration being reached between 24 to 48 hours of life.[1]

Late-onset neonatal hypocalcaemia, which is less common than early-onset form, usually occurs towards the end of first and during the second week of life and is often seen in infants fed with high-phosphate milk.[2] According to the classification, our reported case had late-onset neonatal hypocalcaemia, causes like high-phosphate load, primary hypoparathyroidism, hypomagnesemia and maternal hyperparathyroidism should be considered.

Clinical presentations of neonatal hypocalcaemia could be quite variable and may be confused with other neonatal conditions like sepsis. Common clinical features of neonatal hypocalcaemia include poor feeding, lethargy, tremor, apnoea, cyanosis and seizure.[1,2] Although the classical signs of peripheral motor nerves hyper-excitability are uncommon in newborn,[1] our reported case did present with left-sided facial twitching before frank seizure occurred.

Suspicion of hypocalcaemia should be confirmed with the measurement of serum calcium level. The diagnostic workup for neonatal hypocalcaemia consists of history, physical examination and relevant investigations (Table 3). History of maternal health (e.g. IDDM) and perinatal events (e.g. prematurity) may reveal the cause of neonatal hypocalcaemia. As hypocalcaemia may be a part of DiGeorge syndrome, this syndromal diagnosis which in its full-blown form comprises of congenital heart diseases

Table 1 Causes of neonatal hypocalcaemia[2]

Early Hypocalcaemia (<48 hrs of age)
- Prematurity
- Birth asphyxia/stress
- Infants of diabetic mother

Late Hypocalcaemia (1st week of life)
- High phosphate load (of cow's milk)
- Relative maternal vitamin D deficiency
- Maternal hyperparathyroidism
- Hypomagnesaemia
- Primary hypoparathyroidism

Miscellaneous Disorders (may occur at any time)
- Therapy related
  - Bicarbonate induced
  - Transfusion of citrated blood
  - Furosemide induced
  - White light phototherapy
  - Intravenous lipid administration
- Renal disease

Adapted from Constantine S. Disorders of calcium and phosphorus metabolism. In: Avery ME, Ballard RA, Taeusch HW, eds. Schaffer and Avery's Diseases of the Newborn. 6th ed. W.B. Saunders Company, 1991:929.

Table 2 Mechanisms for the development of neonatal hypocalcaemia[1]

Agent	Problem	Clinical association
Ca (Calcium)	Decreased intake or absorption	Prematurity; malabsorption syndrome
Ca^{2+} (Ionized Calcium)	Increased Ca complex	Chelating agent (e.g. citrated blood for exchange transfusion, long-chain free fatty acid)
Mg (Magnesium)	Decreased tissue store or absorption	Maternal hypomagnesaemia; specific Mg malabsorption
PO_4 (Phosphate)	Increased	Endogenous and exogenous (e.g. dietary, enema) phosphate loading
pH	Increased	Respiratory or metabolic alkalosis (i.e. shifts Ca from ionized to protein-bound fraction)
Parathyroid Hormone	Decreased production	Maternal hyperparathyroidism; hypoparathyroidism; DiGeorge syndrome; Hypomagnesaemia
Calcitonin	Increased	Infant of diabetic mother, birth asphyxia, prematurity
1,25-dihydroxyvitamin D	Decreased end-organ responsiveness	Prematurity

Adapted from Koo WWK, Tsang RC. Calcium and magnesium homeostasis. In: Avery GB, Fletcher MA, MacDonald MGJB, eds. Neonatology: Pathophysiotherapy and Management of the Newborn. 4th ed. Philadelphia: J.B. Lippincott Company, 1994:592.

Table 3 Diagnostic workup for hypocalcaemia[3]

History

- Familial
- Pregnancy (e.g. maternal illness such as diabetes mellitus and hyperparathyroidism; intrapartum events; infant's gestational age
- Dietary intake of infant

Investigations

- Serum Ca, Mg, PO_4, Ca^{2+}, glucose
- Vitamin D metabolites
- Parathyroid hormone
- Calcitonin
- Acid-base balance
- ECG
- Chest X-ray (thymic shadow, aortic arch position)
- Urine drug screen
- Others (e.g. malabsorption workup, lymphocyte count, T-cell numbers and function, maternal and family screening)

Adapted from Koo WWK, Tsang RC. Neonatal calcium and phosphorus disorders. In: Lifshitz F, ed. Pediatric Endocrinology: A Clinical Guide. 2nd ed. New York: Marcel Dekker, 1990:569.

(especially conotruncal cardiac defects), hypocalcaemia, facial dysmorphism (lateral displacement of inner canthi, short palpebral fissures, broad nasal bridge, squaring of nasal root, hypoplastic alae nasi, short philtrum, low-set and malformed ears with hypoplastic earlobes) and immunodeficiency (due to failed thymic development) should not be overlooked.

Investigations for neonatal hypocalcaemia include the measurements of serum total and ionised calcium, phosphate, magnesium, vitamin D metabolites, calcitonin and parathyroid hormone. Phosphate imbalance, hypoparathyroidism, hypomagnesaemia, increased calcitonin, intestinal malabsorption are all associated with hypocalcaemia. Serum albumin level influences the

measured total calcium level as majority of protein-bound calcium is attached to albumin. Change in acid-base balance also affects the calcium-albumin binding and alkalosis will lead to reduction in ionised calcium level. Prolonged QTc interval in electrocardiogram (ECG) could be seen in infants with low ionised calcium. Familial and maternal calcium level and parathyroid status may also affect the neonatal calcium level and should therefore be screened in workup for neonatal hypocalcaemia.

Neonatal hypocalcaemia due to maternal hyperparathyroidism, first described by Friedrichsen in 1938, is a well-known but rare condition. Maternal hypercalcaemia due to raised parathyroid hormone level (PTH) will lead to further increase in placental calcium transfer and foetal hypercalcaemia which in turn, will suppress the foetal parathyroid function. Because of the cessation of maternal trans-placental calcium supply after delivery and continued foetal parathyroid suppression, infant will develop hypocalcaemia gradually, resulting in late-onset neonatal hypocalcaemia.[2,4] Patient suffered from this condition has hyperphosphataemia and low parathyroid hormone level in addition to hypocalcaemia. Hypomagnesaemia is observed in some infants of hyperparathyroid mother as in our reported case, but the exact mechanism for hypomagnesaemia is uncertain.

This condition is more prominent in infant who is fed with cow's milk formula because of its high phosphate content. In breast-fed infant with the same condition, mother's low serum and milk phosphate level might help in increasing the milk calcium-phosphorus ratio above the level as observed in healthy women, and hence protecting the infant from hypocalcaemia in early infancy. Hanukoglu et al (1988) reported a case with same condition presenting with tetany at 4 months of age during the time of transition from breast to formula feeding.[5] In our reported case, the infant's symptoms occurred during the transition from mixed breast and formula feeding to exclusive formula milk feeding. However, as neonate with hypocalcaemia due to maternal hyperparathyroidism usually presents at the same period of life, whether the change of milk formula in our patient is related to the onset of symptoms still could not be ascertained.

Management of neonatal hypocalcaemia consists of the acute management of symptomatic cases (e.g. seizure) and the use of calcium, low phosphorus formula and vitamin D supplement.

Intravenous administration of calcium salts (elemental calcium ~ 10-20 mg/kg/day in form of calcium gluconate or calcium chloride infused over 10-30 min.) is an effective and rapid means to revert hypocalcaemia and its symptoms in case of emergency. Continuous cardiac monitoring is essential during intravenous administration and injection should be discontinued if there is any sign of bradyarrhythmia or once the desired clinical outcome is obtained.[2] Maintenance intravenous or oral calcium (elemental calcium ~ 20-80 mg/kg/day) should then be continued until the calcium level has remained consistently in normal range.

Dietary factors play a role in late-onset neonatal hypocalcaemia and measures should be taken to reduce the phosphate load and increase calcium-phosphorus ratio of feeding.[2,5] Milk formula with low phosphorus (*Nan I*: Calcium 420 mg/L; Phosphorus 210 mg/L) was chosen for our patient and together with the oral calcium supplement, the calcium-phosphorus ratio in feeding was 4:1 in our reported case.

Vitamin D and its metabolites have the effect of increasing serum calcium and phosphate by stimulating intestinal absorption, mobilisation from bone and reducing renal excretion. They are used in maintenance therapy for chronic conditions that cause hypocalcaemia. However, there are no consensus for the types and the dosage of vitamin D use in treatment. Jacobsen et al (1978) recommended the use of 1,25-dihydroxyvitamin D or its analogues with calcium to treat neonatal hypocalcaemia associated with maternal hyperparathyroidism as they found serum PTH and 25-hydroxyvitamin D concentrations increased markedly before serum calcium level returned to normal perhaps indicating an inability to convert 25-hydroxyvitamin D to the metabolically active 1,25-dihydroxyvitamin D during hyperphosphataemic state.[4] Ergocalciferol (Vitamin D_2) is chosen as the form of vitamin D supplement in our case as it has less toxicities like hypercalcaemia, hypercalciuria and impaired renal function than the more polar and water-soluble vitamin D metabolites[5] (25-hydroxy vitamin D, 1-alpha-hydroxy vitamin D and 1,25-dihydroxy vitamin D). High initial dose of vitamin D were used in some other published case reports (1,200 IU per day[4] and 12,000 IU per day[6]) after acute management of hypocalcaemia. Physiologic dose of vitamin D at 400 IU per day was used in our patient and it worked normally as higher dosage. Again, there is no consensus for the duration of vitamin D treatment. To avoid vitamin D intoxication due to prolonged or excessive treatment, urine and blood for calcium should be monitored to look for hypercalciuria and hypercalcaemia and clinical signs of hypercalcaemia like nausea and vomiting, constipation and polyuria should not be overlooked.

Tseng et al (2001) reported four cases of neonatal

hypocalcaemia due to hypoparathyroidism and of these four cases, two patients' mother were subsequently found to have hyperparathyroidism.[7] In our reported case, investigations revealed hypocalcaemia, hyperphosphataemia, hypomagnesaemia and inappropriately low parathyroid hormone level indicating neonatal hypoparathyroidism. Further investigations of patient's asymptomatic mother found hypercalcaemia, hypophosphataemia and increased parathyroid hormone level due to parathyroid adenoma. These explained all the biochemical findings and clinical outcome of our case. Therefore, evaluations of both neonatal and maternal parathyroid status are indicated in order to rule out maternal hyperparathyroidism as a cause of neonatal hypocalcaemia.

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