eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Late Onset Hypocalcemia Caused by Hypovitaminosis D

Dini Anggini[1*], Eka Agustia Rini[2]

[1,2] Faculty of Medicine, Andalas University, Padang, Indonesia

ARTICLE INFO

Keywords:
Hypocalcemia
Hypovitaminosis D
Seizures

***Corresponding author:**
Dini Anggini

E-mail address:
dear_dini14@yahoo.co.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/bsm.v5i10.415

ABSTRACT

Background: hypocalcemia is a common metabolic problem in neonates and infants that can be life threatening. The incidence of hypocalcemia leads to complications and developmental disorders in children. **Case presentations:** A 1 month-old boy with hypovitaminosis D and a history of recurrent hypocalcemia since one week of age. The patient had repeated seizures at the age of 7 days without fever and hypoglycemia, the overall physical examination was within normal, the results of the lumbar puncture were within normal limits. Laboratory examinations at that time showed low of serum calcium, urinary calcium, calcium ion and vitamin D levels, while magnesium, phosphorus and parathyroid hormone (PTH) levels were within normal limits. The patient was diagnosed with late onset hypocalcemia caused by hypovitaminosis D. The patient was given vitamin D therapy, calcium lactate, and intravena calcium correction was performed. **Conclusion:** late onset hypocalcemia occurring after the first 7 days of life was associated with hyperparathyroidism, high phosphate formula administration, DiGeorge syndrome, hypomagnesemia, and vitamin D deficiency.

1. Introduction

Hypocalcemia is a common metabolic problem in neonates and infancy. Neonatal hypocalcemia can be a potentially life-threatening condition[1]. The incidence of neonatal hypocalcemia varies. Data on incidence and prevalence in the neonatal period are limited. A study conducted on 100 neonates in India found the prevalence of hypocalcemia was 76% with hypovitaminosis D found in 88% of cases[2].

The risk of neonatal hypocalcemia is also greater in infants of diabetic mothers and infants with perinatal asphyxia. The severity of hypocalcemia is greater in infants who also have hyperphosphatemia, hypomagnesemia, and vitamin D deficiency or insufficiency[3].

Late-onset hypocalcemia is more common in infants in developing countries where infants are fed cow's milk or formula containing high amounts of phosphate than in countries where infants are fed breast milk or formula containing low amounts of phosphate[4]. There is an increase in late onset hypocalcemia in neonates, especially in neonates born in winter and spring[5].

Hypocalcemia is an important clinical sign that is often missed. Therefore, it is important to identify risk factors, prevention, early identification, and metabolic support for sick neonates[6,7].

2. Case Presentation

A 23 day-old boy was referred to a regional hospital with the diagnosis of recurrent hypocalcemia.

The patient had repeated seizures throughout the body since 7 day old, the frequency was 5-10 times/day, the duration was ± 30 seconds, the eyes were blinking, the legs and arms were like pedaling a bicycle, the child was conscious after the seizure, the seizures

were not accompanied by fever, the blood sugar was within normal during the seizure. This was the first episode of seizure. There was no fever, nor a history of previous fever. There was no cough, runny nose, nor shortness of breath. There were no signs of bleeding in the skin, gums, nose, and gastrointestinal tract. There was no vomiting, nor history of the previous vomiting. The child had no history of anemia. Vitamin K injection was given at birth. There was a history of jaundice at the age of 4-9 days, the jaundice disappeared on its own without phototherapy. During treatment in the NICU, the lowest blood calcium was 5 mg/dl and the highest was 8.3 mg/dl, the patient received repeated intravena calcium correction.

The patient was born through cesarean section due to a previous cesarean section and macrosomia. The child was full-term with a birth weight of 4900 grams, a birth length of 52 cm, and immediately cried at birth. The mother had obesity and was 38 years old when she had pregnant. The mother had no history of diabetes mellitus before, but was known to suffer from hypovitaminosis D with a vitamin D level of 12.7 ng/mL and calcium ion of 1.17 mmol/L. The mother was taking vitamin D supplementation at the time the child was referred to the hospital.

Physical examination was performed when the patient was admitted to the hospital at the age of 23 days. His general condition was good, alert and the blood pressure, pulse rate, respiratory rate, body temperature were all within normal limits. The nutritional status was good with a bodyweight of 4.5 kg, body height of 52 cm. The child did not appear anemic, nor cyanosis. There was no edema, nor jaundice.

The head shape was round and symmetrical, with a head circumference of 35 cm, the major fontanelle was still open and palpable flat. The hair was black and was not easy to fall out. The sclerae were not icteric, the conjunctivae were not anemic. The pupil was isochoric with a diameter of 2 mm for both left and right eyes, with normal light reflexes. The mouth and lips were wet. The tonsils were T1-T1 in size and were not hyperemic. There were no abnormalities found in the ears and nose. There were no palpable lymph nodes. In the chest examination, the heart and lungs were within normal limits. The abdominal and genital examinations were within normal limits, with no bowing legs found in the extremities. Neurological examination was within normal limit.

The head and urology ultrasound was within normal. The results of the lumbar puncture were not in accordance with meningitis, on the investigation of hypocalcemia at that time, the urinary calcium was 14.3 mg/24 hours (reference value: 100-320 mg/24 hours); calcium ion was 0.17 (reference value: 1.17-1,3); PTH was 11.2 pg/ml (reference value: 10-65 pg/mL); blood calcium was 6.3 mg/dl (reference value: 8.1-10.4 mg/dl); vitamin D level was 21.4 ng /ml (reference value: 30-100 ng/mL); magnesium was 1.7 mg/dl (reference value: 1.6-2.6mg/dl); phosphorus was 7 mg/dl (reference value: 3-7.5 mg/dl). The lab results showed hypocalcemia and hypovitaminosis D. The patient was diagnosed with late onset hypocalcemia due to hypovitaminosis D with macrosomia. The patient was given vitamin D supplementation of 1x2000 IU, calcium lactate 3x100mg, and IV calcium correction (if serum calcium <7.5 mg/dl). The patient had improved after vitamin D administration and was discharged from the hospital after 14 days. Patients routinely received vitamin D therapy 1x2000 IU, calcium lactate 3x100 mg, and routine check-ups at the pediatric endocrinology clinic every month.

In the long-term observation of 4 semesters, the child had well growth and development according to his age. During the observation, the child never had a seizure and there were no signs and symptoms of rickets. He had good nutritional status with a growth rate of 25 cm/year (P97) in the first year and 10 cm/year (P75) in the second year. The child had completed basic and booster immunizations. Routine calcium examination was carried out every 2-3 months, the results were within normal limits. On repeat blood examination, which was carried out when the child was 20 months old, the results showed hemoglobin of 12 g/dl, leukocytes of 7600/mm^3, platelets of 410,000/mm^3, hematocrit of 36.5%, calcium ion of 1.31 mmol/L, 25-Hydroxivitamin D level of 47,4 ng/ml (sufficiency), urea of 12 mg/dl, creatinine of 0.4 mg/dl. Furthermore, vitamin D supplementation of 1x2000 IU

was given every three days and calcium lactate of 3x100mg was given per day. After 6 months, the child underwent the 25-(OH)D test again.

3. Discussion

Hypocalcemia is a condition that can cause serious problems, especially in newborns. Hypocalcemia often occurs in newborns which can be caused by the delay in the function of parathyroid hormone in calcium metabolism[8].

Neonatal hypocalcemia is a potentially life-threatening condition, with its prevalence varying according to gestational age, maternal, and infant comorbidities, and perinatal factors[3]. In term infants, hypocalcemia is defined as a total serum calcium concentration of < 2.0 mmol/L (<8.0 mg/dL) or <1.75 mmol/L (<7.0 mg/dL) in preterm infants[8,10]. Hypocalcemia in neonates is classified into 3 groups. First, early onset hypocalcemia (during the first week of life); the second is late onset hypocalcemia (occurs anytime after the first week of life); and lastly, there is a paradoxical occurrence where neonatal hypocalcemia often occurs asymptomatically[9,10].

The main cause of hypocalcemia in infants of diabetic mothers is hypomagnesemia in both mother and baby due to increased maternal urinary magnesium excretion during pregnancy. Hypomagnesemia will cause functional hypoparathyroidism in infants. Maternal hyperparathyroidism can suppress fetal PTH synthesis and interfere with the PTH response to postpartum hypocalcemia[9].

Maternal vitamin D deficiency is a common problem worldwide[11]. Neonatal serum vitamin D concentrations depend on maternal vitamin D status and sun exposure[12,13]. Thus, it is hypothesized that there is a relationship between late onset hypocalcemia in newborns and maternal vitamin D levels. It is important to measure the levels of 25-(OH)D and intact parathyroid hormone (iPTH) in maternal-neonatal, especially those at risk[5].

The patient had repeated generalized seizures since the age of 7 days with a frequency of 5-10 times/day with a duration of ± 30 seconds. The overall physical examination was within normal and no sign of meningitis. At the time of presentation, serum calcium, urine calcium, calcium ion, and vitamin D levels were low, while magnesium, phosphorus and parathyroid hormone (PTH) levels were within normal limits. Based on the patient's onset of recurrent seizures, this corresponds to late onset hypocalcemia. This is in accordance with a study conducted on 100 neonates who experienced recurrent hypocalcemia in India in 2018 where 45% were late onset hypocalcemia with hypovitaminosis D found in 88% of cases[2]. Risk factors, in this case presentation, were macrosomic infant, obese mother, and no vitamin D and calcium supplements during pregnancy. Furthermore, there was a history of maternal hypovitaminosis D[14].

Management

The basic treatment for hypocalcemia is calcium replacement and treatment options may vary based on the symptoms and degree of hypocalcemia. In newborns with tetanus-like symptoms or seizures, IV administration 1-2 mL/kg/dose using 10% calcium gluconate is given by slow bolus for acute treatment of hypocalcemia.[9,10]. During recurrent seizures, the patient received IV calcium correction with 10% calcium gluconate.

In patients with vitamin D deficiency, vitamin D replacement of 1000 to 2000 IU/day is recommended. The response will not be achieved if treatment of hypocalcemia is carried out without treating hypomagnesemia first. In infants with excessive phosphate loads, the goal of treatment is to lower serum phosphate levels. Therefore, high-phosphate feeding should be avoided and infants should be fed a high-calcium and low-phosphate diet either with breast milk or formula with a low phosphate content[9,15].

The American Academy of Pediatrics recommends vitamin D supplementation of 400 IU/day in neonates from birth to 2 years of age, while the Endocrine Society recommends a 25-(OH)D level of 30 ng/ml (50 nmol/L), but to prevent deficiency, they recommend between 40 – 60 ng/mL in both children and adults[6].

Administration of 400 IU of vitamin D has been shown to maintain serum 25(OH)D concentrations > 50

nmol/L in breastfed infants. Thus, for all newborns, vitamin D supplementation of 400 IU is recommended until one year of age and it is recommended that supplementation be started within the first few days of life[16].

Fortified cow's milk is not recommended for children younger than 12 months because it increases the risk of gastrointestinal bleeding and the milk contains too much protein and minerals. For children who have started to consume food, vitamin D can be obtained from fish, eggs, yoghurt, cereals, and juices[16,17].

Neonates of mothers with vitamin D deficiency will experience vitamin D deficiency. This occurs because there is no endogenous production of vitamin D and all depends on transplacental migration[14,16,18]. However, to increase the vitamin D content of breast milk, very large doses are needed to be given to nursing mothers. Therefore, infants are advised to be supplemented with 400 IU daily and mothers continue to take 600 IU daily for their own vitamin D needs[16].

In this case presentation, at the final follow up, the patient was 2 years old with a good final nutritional status. The child's developments were in accordance with his age. The last blood examination showed 25(OH)D levels and calcium ion level were within normal limit.

The recommended dose of vitamin D for neonates with vitamin D deficency is 1000 IU/day, 2000-3000 IU/day for infants and toddlers, and 3000-5000 IU/day for children and adolescents aged 1-18 years[19]. Ganmaa et al, conducted a study of giving vitamin D supplementation to children for 6 months at a dose of 800 IU/day showed significant results in increasing vitamin D levels and increasing children's height[20]. Therapy for vitamin D and calcium deficiency is carried out for a minimum of 3 months. If there is no radiological or biochemical improvement after 3 months, the patient should be investigated for non-nutritional rickets[7].

4. Conclusion

Neonatal hypocalcemia is a potentially life threatening condition. Hypocalcemia is an important clinical sign that is often missed. Therefore, it is important to identify risk factors, prevention, early identification, and metabolic support for sick neonates. Late-onset hypocalcemia occurring after the first 7 days of life is associated with hyperparathyroidism, high phosphate formula administration, DiGeorge syndrome (chromosomal deletion 22q11.2), hypomagnesemia, and vitamin D deficiency.

5. References

1. Cho WI, Yu HW, Chung HR, Shin CH, Yang SW, Choi CW, et al. Clinical and laboratory characteristics of neonatal hypocalcemia. *Ann Pediatr Endocrinol Metab*. 2015; 20: 86.
2. Anitha A, Mustafa M. Prevalence of neonatal hypocalcemia and its relation to supplementation. *Int J Curr Res Biol Med*. 2017; 4: 11–8.
3. Thomas TC, Smith JM, White PC, Adhikari S. Transient neonatal hypocalcemia: presentation and outcomes. *Pediatrics*. 2012; 129: 1-5.
4. Malhotra Y, Campbell DE, Bowden SA. Pediatric Hypocalcemia [Internet]. 2016. Available from: https://emedicine.medscape.com/article/921844-overview.
5. Do HJ, Park JS, Seo JH, Lee ES, Park CH, Woo HO, et al. Neonatal late-onset hypocalcemia: is there any relationship with maternal hypovitaminosis D? *Pediatr Gastroenterol Hepatol Nutr*. 2014; 17, 47–51.
6. Bosnjak I, Raguz MJ. Frequency of neonatal hypocalcaemia and its correlation with risk factors. *Clin Mother Child Heal*. 2017; 14: 1-5.
7. Elsary AY, Elgameel A, Mohammed WS, Zaki OM, Taha SA. Neonatal hypocalcemia and its retation to vitamin D and calcium supplementation. *Saudi Med J*. 2018; 39(3): 247-53.
8. Tohaga E, Budhi K, Wijayahadi N. Hubungan antara derajat asfiksia dengan beratnya hipokalsemia pada bayi baru lahir. *Sari Pediatr*. 2016; 16: 29.

9. Vuralli D. Clinical approach to hypocalcemia in newborn period and infancy: Who should be treated?. *Int J Pediatr*. 2019; 1–7.
10. Jain A, Agarwal R, Sankar J, Deorari A, Paul V. Hypocalcemia in the newborn. *Indian J Pediatr*. 2010; 77: 1123–8.
11. Pligt P, Willcox J, Szymlek-Gay EA, Murray E, Worsley A, Daly RM. Associations of maternal vitamin D deficiency with pregnancy and neonatal complicaions in developing countries: a systematic review. *Nutrients*. 2018; 10: 1-22.
12. Wierzejska R, Jarosz M, Kleminska-Nowak M, Romaszewska M, Sawicki W, Bachanek M, et al. Maternal and cord blood vitamin D status and anthropometric measurements in term newborns at birth. *Frontiers in Endocrinology*. 2018; 9: 1-6.
13. Oktaria V, Graham SM, Triasih R, Soenarto Y, Bines JE, Ponsonby AL, *et al*. The prevalence and determinants of vitamin D deficiency in Indonesia infants at birth and six months of ago. *Plos One*. 2020; 15: 1-15.
14. Fiscaletti M, Stewart P, Munns CF. The importance of vitamin d in maternal and child health: A global perspective. *Public Health Rev*. 2017; 38: 1–17.
15. Gomella TL, Eyal FG. Calcium disorder. In: Gomella's Neonatology. 8th ed. New York: McGraw-Hill Education. 2020; 833–8.
16. Khadilkar A, Khadilkar V, Chinnappa J, Rathi N, Khadgawat R, Balasubramanian S, et al. Prevention and treatment of vitamin d and calcium deficiency in children and adolescents: Indian academy of pediatrics guidelines. *Indian Pediatr*. 2017; 54: 567–73.
17. Marks K. Infant and toddler nutrition [Internet]. Vol. 44, Australian Family Physician. 2015; 886–9. Available from: https://www.cdc.gov/nutrition/infantandtoddlernutrition/index.html
18. Hegazy AM, Shinkar DM, Mohamed NR, Gaber HA. Association between serum 25 (oh) vitamin d level at birth and respiratory morbidities among preterm neonates. *J Matern Neonatal Med*. 2018; 31: 2649–55.
19. Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, et al. Vitamin D supplementation guidelines. *Journal of Steroid Biochemistry & Molecular Biology*. 2016; 1-11.
20. Ganmaa D, Struart JJ, Sumberzul N, Ninjin B, Giovannucci E, Kleinman K, et al. Vitamin D supplementation and growth in urban mongol school children: results from two randomized clinical trials. *Plos One*. 2017; 12(5), 1-13.