Late-onset neonatal hypocalcemia in a 9-days-old baby because of vitamin D deficiency and hypoparathyroidism: a case report

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ABSTRACT

Background: Neonatal hypocalcemia is a metabolic abnormality commonly reported. Late onset hypocalcemia usually manifests after 7 days and requires a long-term therapy. Neonatal hypocalcemia due to hypoparathyroidism can manifest as life-threatening seizures or tetany. Initial management is important to prevent any complication due to this condition. However, the initial management to correct hypocalcemia with the administration of calcitriol, high dose intravenous and oral calcium may take longer to achieve because of hypoparathyroidism.

Case summary: We report a case of late onset neonatal hypocalcemia in a nine-days-old baby. He was born on the 35-36 week of gestational age by Caesarean section, without asphyxia nor neonatal infection. The baby had a refractory seizure with low serum calcium and magnesium, high phosphate, normal alkaline phosphatase (ALP) and low calcium creatinine urine ratio. His 25-hydroxy vitamin D (25-OHD) total was as low as 12.9 ng/mL. And, he has a low level of parathyroid hormone (PTH). Adequate correction for hypocalcemia and hypomagnesemia failed to maintain calcium and magnesium to their normal value. Oral calcium gluconolactate and carbonate were added after calcitriol supplementation, but seizure still noticed. After magnesium oxide supplementation was given, another seizure had never occurred. A long-term follow-up on vitamin D and calcium level were required.

Conclusion: In a hypocalcemic newborn patient, assessment of the magnesium, vitamin D, and PTH status are needed.

Keywords: neonatal, hypocalcemia, parathyroid, vitamin D


INTRODUCTION

Electrolyte imbalance occurs frequently in neonates. One of the essential electrolytes is calcium. Calcium ion is crucial for many biochemical processes including blood coagulation, neuromuscular excitability, cell membrane integrity, and many of the cellular enzymatic activities. A major part of the body calcium exists in bones and muscles (99%) and the rest of the calcium is present in the extracellular fluid (1%). Around 40% of calcium binds with albumin and becomes crystal with anion phosphorus and therefore becomes inactive. But, 50% exists in a free ionized form. Healthy term infants undergo a physiological lowest point in serum calcium by 24-48 hours of age. The nadir may drop to hypocalcemic level in high-risk neonates, for example in the infants of diabetic mothers, preterm infants, and infants with perinatal asphyxia.1-3

Neonatal hypocalcemia is classified into early onset hypocalcemia which presents within 72 hours after birth and requires treatment with calcium supplementation for at least 72 hours. In contrast, late onset hypocalcemia usually presents after 7 days and requires long-term therapy.4 Hypocalcemia is an uncommon problem in term and near-term neonates. A study showed a significant increase in urinary calcium to creatinine ratio and fractional excretion of sodium in full-term neonates who were treated with gentamicin (2.5 mg/kg of body weight every 12 hours). These changes were not seen in infants who received amikacin or netilmicin. Birth asphyxia is associated with lower serum calcium level in the newborn period. Other factors such as increased bicarbonate therapy, phosphate loads, and functional hypoparathyroidism are possible pathogenetic mechanisms for the hypocalcemia.2

Neonatal hypocalcemia due to hypoparathyroidism is rare and may manifest as life-threatening seizures or tetany. The initial management is by administering calcitriol and high dose calcium. But hypocalcemia correction in hypoparathyroidism using intravenous and oral calcium takes longer to achieve. The use of recombinant parathyroid hormone to correct hypocalcemia due to hypoparathyroidism has been proposed, but still lacking supporting evidence.6,8 A proper handling of late-onset neonatal hypocalcemia will have a good outcome.

CASE PRESENTATION

March 25, 2016

A 2900 gram, preterm male neonate with gestation age 35-36 week was born to a gravida 2 mother by a Caesarean section. He had a normal extra-uterine transition (Apgar score was 8 and 9 at the 1st and...
5th minute of life). The head circumference was 33 cm, chest circumference 30 cm, and birth length 46 cm. He was found normal in other physical examinations, urinated and defecated 7 hours after birth. He had vitamin K1, Hepatitis B vaccination, and oral polio vaccine before his discharge in the next two days. During the pregnancy, the mother had not had a fever, a high blood pressure, a whitish discharge, nor a urinary tract infection.

April 2, 2016
The mother came to our hospital complaining that her 9-days-old baby appeared yellowish since early in the morning. He had breastmilk and formula (cowmilk). She was alarmed because her baby appeared like having a seizure when he pooped. On physical examination, the baby had a good weight increment of 200 gram and he had icterus Cramer III. His total bilirubin was 14.11 mg/dL and direct bilirubin 1.17 mg/dL. After a single phototherapy for two days, luminal 8 mg b.i.d., and multivitamin 0.3 ml q.d., his icterus was disappearing. The total bilirubin became 6.10 mg/dL and direct bilirubin 1.08 mg/dL.

April 5, 2016
The patient was brought to our Emergency Department early in the morning. The mother was concerned because he would not drink, and he had been crying since last evening and blinking frequently. On our observation, general condition was good. There was no fever, lethargy, nor poor feeding. The clinical findings were unremarkable in the neonate. The baby was assessed with involuntary movement and low calorie intake. The CT scan (figure 1) was negative for mass effect, intracranial bleeding, nor calcification in brain parenchymal. The left and right mastoid bones were normal. The initial blood sugar test was normal. However, the calcium serum was found low (total 4.5 mg/dL), and he had a low magnesium 1.36 mg/dL. He was screened negative for sepsis and the blood culture was sterile.

He was given 60 mg phenobarbital, ampicillin 150 mg intravenous (i.v.) t.i.d., and gentamicin 15 mg 36 hourly. A focal seizure was still reported by the parents so that phenytoin 50 mg was added. Intravenous correction for calcium was added. He was given 1.4 ml (0.11mmol/kg of body weight) with D10% 5 ml infusion drip for 2 hours, and then 5.6 ml (0.44mmol/kg of body weight) with D10% until a total of 20 ml drip for 8 hours. He received a maintenance dose for phenytoin and phenobarbital. After the i.v. correction, the serum calcium was 6.6, and magnesium 1.29 mg/dL. The maternal Vitamin D1 and 25-hidroxy vitamin D (25-OHD) were not examined. He was consulted to the neurology department and was assessed with a convulsion in observation because of fetal distress with generalized hypoxia and ischemia in the brain. The phenytoin was stopped. But, the calcium i.v. correction was continued for another 8 hours.

April 6, 2016
There was no seizure. His serum calcium was 7 mg/dL and his serum magnesium was still low 1.66 mg/dL. The i.v. treatment was stopped and his oral phenobarbital intake was tapered.

April 8, 2016
The patient was discharged from our hospital with oral phenobarbital 15 mg q.d. and a multivitamin 2.5 ml q.d.

April 9, 2016
The baby was brought again to our hospital. His mother complained that he had had an inconsolable crying and his face seemed flushed after he was discharged from the hospital. The physical examination was within normal limits. The baby was assessed to have an abdominal colic. He was admitted and given phenobarbital 0.5 ml b.i.d., probiotic 5 drops q.d., vitamin 1 capsule b.i.d., and an enteral feeding.

On the fourth hour of his hospitalization, he had an afebrile seizure involving both arms and his face for about 1 minute, and the seizure stopped by itself. His blood glucose was normal 108 mg/dL. The baby was treated with an i.v. fluid which contains glucose and electrolyte for calcium about 2 ml per body weight for a day. He was also given an oral phenobarbital. He was checked for electrolyte imbalance, complete blood count, and infection markers.

April 10, 2016
He had a 1-minute partial afebrile seizure and was suspected with an epileptic seizure by a child neurologist. He was planned for an electroencephalography (EEG). He had a low serum calcium 5.4 mg/dL, low magnesium 1.46 mg/dL, inorganic phosphor 11.3 mg/dL, sodium 135 mmol/L, potassium 5.6 mmol/L, chloride 96 mg/dL. But, his blood count was normal. He was corrected for calcium 2 ml per body weight in 20 ml D10% for 10 hours.

April 11, 2016
The patient had a focal seizure twice. His anti-seizure was given in an i.v. drip. The blood test showed the serum calcium was decreased by 0.55 and magnesium 1.41 mg/dL. The EEG showed a multifocal spike wave without hypofunction. Afterward, the patient was given an i.v. bolus of calcium gluconate followed by an i.v. drip correction. A child endocrinologist prescribed a 1,25-hidroxy vitamin D,
an active metabolite of vitamin D (in calcitriol 0.25 mcg q.d.), and planned for vitamin D, thyroxine, and parathyroid hormone (PTH) examination. MgSO4 would be given if the seizure persisted.

April 12, 2016
He had another seizure so that carbamazepine (15 mg b.i.d.) and vitamin D 1 capsule q.d. were added. After i.v. correction, the serum calcium increased to 5.3 mg/dL, magnesium increased to 1.46 mg/dL. His FT4 was low 0.89 ng/dL and his TSHs was 2.15 micro U/mL.

April 15, 2016
The baby still had a seizure and became lethargic on the next three days, as shown in figure 2. The seizure stopped after he had i.v. correction and a bolus for calcium gluconate and magnesium correction with MgSO4 0.8 ml in 10 mL D10% via a central venous catheter. Figure 3 showed the location of the catheter tip. The serum calcium increased to 6 mg/dL, magnesium 1.88 mg/dL. No seizure was present after the correction so that the anticonvulsant was tapered. The serum calcium was 6.7 mg/dL, magnesium 1.71 mg/dL.

He had another focal seizure after the phenobarbital i.v. was stopped. At that time, the calcium

Figure 1  Patient's CT scan showed no mass effect, no bleeding, no calcification in brain parenchymal, and left and right mastoid bones were normal.

Figure 2  The picture of the baby in an incubator when he was 19 days old.

Figure 3  The X-ray showed the heart, lungs, and the structures in mediastinum were normal, with the tip of the central venous catheter at the umbilical region. It was taken to evaluate the position of the catheter.
was 6.5 mg/dL and magnesium 1.64 mg/dL. The urine electrolyte for 24 hours showed urine calcium 0.01 mmol/24 hours. The patient still had a few seizures after an intake of oral calcium gluconolactate and calcium carbonate 50 mg/kg of body weight q.d. The serum calcium failed to rise to 8 mg/dL. Carbamazepine was also given with a dose of 15 mg/kg body weight. Alkaline phosphatase (ALP) was within normal range 259 U/L. The serum magnesium, PTH, and vitamin D was low. PTH intact was 10.18 pg/mL, 25-OHD total was 12.9 ng/mL.

**April 22, 2016**

He had another general seizure after seven days free from seizure. Serum calcium was 6 mg/dL, magnesium 1.62 mg/dL. He received one unit of packed red blood cell transfusion for anemia. The hemoglobin was 9.5 gr/dL. After magnesium oxide administration by the endocrinologist, the seizure had never occurred anymore. The patient had never had another seizure during epilepsy treatment, oral calcitriol, and oral magnesium supplementation.

**DISCUSSION**

The most common cause of seizure in the newborn period is hypoxic-ischemic encephalopathy in term infant which onset 24 hours after birth. Infections are also the most common cause of neonatal seizures in the late first week and during the second week of life. Intractable seizures unresponsive to usual therapy may result from congenital pyridoxine deficiency and may respond to vitamin B6 replacement. In our case, the seizure occurred in the second week of life. The pregnancy history was negative for fever, whitish discharge, urinary tract infection, greenish amnion, and early amniotic fluid ruptured as risk factors for baby infection. The patient born vigorously with Apgar score 8-9 and no seizure witnessed within 24 hours of life. Recurrent seizure was noticed but responded to calcium and magnesium therapy. He never had pyridoxine supplementation as a therapy.

Based on the time of presentation, Neonatal hypocalcemia is classified into early and late. Early neonatal hypocalcemia is defined as occurring in the first 48 hours of life and usually symptomatic. And, if it does not respond to an adequate dose of calcium, it should be considered as late onset hypocalcemia. The differential diagnosis includes prematurity, ill neonates, intrauterine growth retardation, and birth asphyxia. About one-third of cases occurred within the first 3 days of life. Late onset neonatal hypocalcemia is generally defined as hypocalcemia presenting as seizures after the 3rd day of life. The differential diagnosis include high phosphate load from formula feeding, hypomagnesemia, hypoparathyroidism (including DiGeorge syndrome, 22q deletion syndrome), disorders of vitamin D metabolism, maternal intake of anti-convulsant (phenobarbitone, sodium phenytoin), maternal hyperparathyroidism, iatrogenic (alkalosis, use of blood products, diuretics, lipid infusions), and metabolic syndrome (Kenny-Caffey syndrome, long chain fatty acyl-CoA dehydrogenase deficiency, Kearns-Sayre Syndrome).

The reported cases of late transient hypocalcemia due to formula-fed was 30:10000 and 10:10000 in breastfeeding babies. The presence of hypocalcemia and an elevated PTH level indicate a possibility of an end-organ resistance to PTH, mimicking pseudohypoparathyroidism.

Our patient had a late onset neonatal hypocalcemia presenting a seizure after the 3rd day of life. Unfortunately, we did not check the maternal vitamin D and the PTH status. The baby was breastfed, but a formula was also added. There was no history of a genetic disorder related to hypocalcemia was found. The hypocalcemia and hypomagnesia were secondary due to hypoparathyroidism and were corrected by calcium and magnesium supplementation.

The etiology of our patient condition was hypoparathyroidism, which low PTH serum concentration caused hypocalcemia and hyperphosphatemia. A secondary hypocalcemia may occur because the end organ response to PTH was blunt. Our patient had a recurrent seizure from secondary hypocalcemia due to hypoparathyroidism with PTH intact 10.18 pg/mL. The low concentration of PTH decreases calcium absorption from distal intestine and kidney, and also decreases the calcium mobilization from bone.

Other studies had demonstrated hypocalcemia related to gentamicin administration. Aminoglycoside has been shown to mimic the effect of calcium and magnesium on parathyroid cells, which would reduce parathyroid hormone secretion. It is associated with the stimulation of the parathyroid calcium-sensing receptor and an increase in calcium and magnesium excretion. Urinary calcium excretion was increased in our patient. However, it was not due to proximal tubular injury. The lowest serum calcium was observed in the early course of gentamicin treatment. The baby was treated with gentamicin 5 mg/kg of body weight for 3 days because he was suspected of sepsis. But, the baby was still hypocalcemic after the aminoglycoside administration was stopped. We did not order any specific examination to check the calcium level in the early course of gentamicin.
A study from a large family in which hypoparathyroidism as an autosomal dominant trait and was linked to chromosome 3q13, the same region containing the calcium sensing receptor (CASR) gene. The affected family members may have mild hypocalcemia (6–8 mg/dl), and relatively few symptoms. Seizures can occur, especially in younger patients, and these often happen during febrile episodes due to intercurrent infection. Uncommon symptoms of hypocalcemia are paresthesia, tetany, and laryngospasm.11,12,15 In our patient, a recurrent seizure was not occurred during febrile episodes. He did not have an infection. It was proven by the normal septic marker and a sterile blood culture. We did not check for a genetic disorder so that we cannot determine the etiology of the hypoparathyroidism.

Even though neonatal hypocalcemia may manifest in hypotonia, poor feeding, stridor and jitteriness, the most alarming one is the seizure activity. Clinical manifestation in the neonatal and early infantile period differ considerably from those in older children because newborns are less able to sustain an organized, generalized epileptiform activity. The seizure in our patient was focal. All other causes were excluded by history, blood analysis, and imaging studies.

The clinical presentation of early-onset neonatal hypocalcemia, symptoms maybe neuromuscular irritability, myoclonic jerk, jitteriness, exaggerated startle.16,18 Our patient had an intractable seizure after 9 days of life, secondary to late onset neonatal hypocalcemia. The baby had a multifocal migratory seizure with neuromuscular irritability at earlier stage like inconsolable crying at his first hospital visit.

The primary predisposing factor of neonatal hypocalcemia is the lack of calcium intake which has been sharply curtailed when compared with that received in utero. The concentration will decrease until it achieves nadir point at 2 days of life in a term babies (7.5–8.5 mg/dL) and will mature at 2–4 weeks.1,4 The calcium concentration falls by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL fall in albumin concentration.1,4 We did not record the calcium from newborn, as we know the decreasing calcium level achieves the nadir point at 2 days of life. From the ninth day of life, the baby always had a low serum calcium but the albumin concentration was never examined. After a calcium correction, the seizure stopped. But, when calcium supplementation was tapered, the seizure reoccurred. The seizure stopped after magnesium supplementation. No heparin was used by the patient nor any acidosis or alkalosis agent.

A study in Iran found 100% of babies born with late onset hypocalcemia were born from mothers with vitamin D deficiency.19 Vitamin D deficiency also occurs in infant with rickets, cholestasis, and lack of sun exposure.11,19,20 We did not record the maternal vitamin D status. The baby was not cholestatic, not suffering from rickets, and not lacking of sun exposure. The lack of PTH decreased calcium absorption in the intestine and calcium absorption in the kidneys. The supplementation of active form of vitamin D is essential for correcting the hypocalcemic condition.

Hypocalcemia unresponsive to an adequate dose of i.v. calcium therapy is usually due to hypomagnesemia. The neonate should receive 2 doses of 0.2 mL/kg of body weight of 50% MgSO4 in 12 hours apart via deep intramuscular injection.10 Our patient was treated with calcium gluconate 0.11 mmol/kg of body weight in 20 mL dextrose 10% in 2 hours and continued with 0.44 mmol/kg of body weight for 8 hours. The patient was still suffered from a focal seizure after given calcitriol 1.25 mcg per day, maintenance oral calcium 50 mg/kg of body weight and magnesium correction with MgSO4. The seizure stopped after a magnesium oxide supplementation.

CONCLUSION

Hypocalcemia in our patient failed to increase PTH secretion. The low PTH decreased calcium absorption from intestine and calcium absorption in renal. Vitamin D supplementation, acute and chronic correction for hypocalcemia, and a supplementation of magnesium and calcium in dietary intake should be given together to improve hypocalcemia. In a hypocalcemic newborn patient, we should assess the magnesium, vitamin D, and PTH status.

REFERENCES


