

Late neonatal hypocalcemic tetany as a manifestation of unrecognized maternal primary hyperparathyroidism

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SUMMARY: Çakır U, Alan S, Erdeve Ö, Atasay B, Şıklar Z, Berberoğlu M, Arsan S. Late neonatal hypocalcemic tetany as a manifestation of unrecognized maternal primary hyperparathyroidism. *Türk J Pediatr* 2013; 55: 438-440.

Maternal primary hyperparathyroidism causing hypercalcemia during pregnancy can suppress fetal and neonatal parathyroid hormone secretion. We report a newborn with transient hypoparathyroidism presented by hypocalcemic seizure and tetany on the 21st postnatal day in whom the final diagnosis was asymptomatic maternal primary hyperparathyroidism. Neonatal hypocalcemia usually occurs early in life in infants of maternal primary hyperparathyroidism, and although it is very rare, further investigation for unexplained late-onset hypocalcemia may reveal this diagnosis.

Key words: neonatal hypocalcemia, neonatal seizure, hypocalcemic tetany, primary hyperparathyroidism, pregnancy, transient hypoparathyroidism.

Primary hyperparathyroidism (PHP) during pregnancy is a very rare event that increases maternal and perinatal morbidity and mortality. PHP in women of childbearing age is estimated to be approximately 8 cases per 100,000 per year. Most cases are diagnosed during pregnancy¹.

Maternal PHP causing hypercalcemia during pregnancy can suppress fetal and neonatal parathyroid hormone (PTH) secretion². As a consequence, transient neonatal hypoparathyroidism can occur in an infant born to a mother with untreated hyperparathyroidism. Transient suppression of fetal parathyroid development may result in severe neonatal hypocalcemia that leads to seizures. As most affected mothers are asymptomatic, neonatal hypocalcemic tetany, which usually develops during the first 72 hours, may be the first manifestation of the underlying maternal PHP³.

We here report a 21-day-old newborn who developed seizure activity due to hypocalcemia associated with maternal PHP, and we discuss this rare entity with reference to the recent literature.

Case Report

A male newborn born to a 27-year-old mother was admitted to the pediatric emergency room with respiratory distress, cyanosis and tetany. The baby was delivered at term by spontaneous vaginal route, with a birth weight of 3300 g, and the perinatal course was uneventful. The baby was fed with breast-milk and remained well until the 21st day of life, when eye blinking and tetany in his arms were noted. On admission to the neonatal intensive care unit, the physical examination was normal except for lethargy and eye blinking, facial grimacing, and tetany. Biochemical analysis revealed hypocalcemia (5.8 mg/dl, N: 9-11 mg/dl) as an etiology of the seizure. Septic work-up including lumbar puncture, other biochemical parameters, cranial tomography, and electroencephalography were all normal. Complete control of the seizure activity was attained in six hours with intravenous calcium and oral phenobarbital treatment.

Screening for the etiology of neonatal hypocalcemia, which was diagnosed on admission, revealed a high serum phosphorus (P) (8.5 mg/dl, N: 4.5-6.7 mg/dl) and normal serum 25-OH D3: 35.1 nmol/L (N: >25 nmol/L) and PTH: 21.5 pg/ml (N: 9-65 pg/

ml) levels. Although hypocalcemia was present, there were no expected increases in serum PTH or vitamin D levels. PTH level in a state of hypocalcemia led us to screen the mother. Maternal serum calcium level was high (11.1 mg/dl, N: 8.6-10 mg/dl) and serum P level was low (2.1 mg/dl, N: 2.7-4.5 mg/dl). Endocrinological evaluation revealed a low serum 25-OH D3 level (13.2 nmol/L, N: >25 nmol/L), but a very high serum PTH level (577 pg/ml, N: 9-65 pg/ml). Therefore, the etiology of neonatal hypocalcemia was transient neonatal hypoparathyroidism due to maternal PHP.

The newborn was started on oral elementary calcium at a dose of 250 mg/kg/day and active vitamin D (calcitriol) at a dose of 50 ng/kg/day. On follow-up, oral calcium supplementation was decreased progressively, and both calcium and active vitamin D were discontinued on the 98th day of life. Vitamin D supplementation at a dose of 400 IU/day was started. His mother was evaluated by the Endocrinology Division, and parathyroid adenoma was detected, and she underwent minimally invasive parathyroidectomy for the adenoma.

Discussion

Most cases of neonatal hypocalcemia occur soon after birth, especially in those high-risk infants with low birth weight, intrauterine growth retardation, diabetic mothers, maternal PHP, and prolonged, difficult deliveries³. Late neonatal hypocalcemia (LNH), which is defined as hypocalcemia observed after postnatal 72 hours, is very unusual and generally related to increased phosphate load, hypomagnesemia, vitamin D deficiency, PTH resistance, primary hypoparathyroidism, maternal hyperparathyroidism, and metabolic syndromes (Kenny-Caffey syndrome, long-chain fatty acyl CoA dehydrogenase deficiency, Kearns-Sayre syndrome), or it is iatrogenic⁴. Conditions with hypocalcemia and normal P in the presence of elevated PTH levels indicate the possibility of an end-organ resistance to PTH, mimicking pseudohypoparathyroidism⁵. Our patient presented with intractable seizures after 21 days of life, secondary to LNH. Seizure due to infantile hypoparathyroidism secondary to maternal PHP as observed in our patient has been reported rarely¹.

Maternal PHP causes suppression of fetal parathyroid glands secondary to an increase in net calcium flux across the placenta to the fetus. This leads to neonatal hypoparathyroidism and hypocalcemia². Increased PTH levels due to parathyroid adenoma were documented in our patient's mother. The role of parathyroid hormone-related peptide (PTHrP) in parathyroid adenoma is uncertain. However, slightly elevated PTHrP concomitant with increased PTH level was reported in primary hyperparathyroidism due to parathyroid adenoma². Despite the effect of PTHrP on fetomaternal calcium homeostasis, serum PTHrP was not measured in our case's mother, because PTHrP could not be totally excluded in the presented case. PTHrP could play a role during pregnancy and the perinatal period as it is produced in the placenta and in fetal parathyroid glands, and it is expressed in maternal milk as well³.

The majority of the mothers with PHP have mild hypercalcemia, whereas about 5% of them are normocalcemic². In almost all reported cases of neonatal hypoparathyroidism caused by maternal PHP, the mothers were found to be hypercalcemic^{1-3,6}. Patients with primary PHP such as our patient's mother are often asymptomatic, even though they are hypercalcemic². The mother was asymptomatic except for recorded chronic constipation on retrospective questioning. Neonatal hypoparathyroidism was the first clue of maternal PHP in our mother-infant couple. If the diagnosis had been missed in the mother, she might have ultimately developed serious complications such as progressive nephrocalcinosis and renal failure.

Though neonatal hypocalcemia may present with symptoms such as hypotonia, poor feeding, stridor, and jitteriness, the most alarming one is the seizure activity. Clinical manifestations in the neonatal and early infantile period differ considerably from those in older children, as newborns are less able to sustain organized, generalized epileptiform activity. As observed in other cases of neonatal hypocalcemia, the seizure activity in our patient was clinically focal. All other causes in our patient were excluded by history, blood analyses or imaging studies.

This report highlights the importance of careful evaluation of neonatal hypocalcemia-

hypoparathyroidism in revealing an unrecognized asymptomatic maternal PHP. Early detection and treatment of the condition prevent subsequent serious complications in both the newborn and the mother. We suggest that in such a case, detailed examination of the mother is essential.

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