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Case Report

Transient hypercalcemia followed by hypocalcemia in a preterm infant after maternal magnesium sulfate therapy

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Highlight

- Hypocalcemia can be preceded by hypercalcemia in neonates after maternal $MgSO_4$.

Abstract. Maternal use of magnesium sulfate has been associated with neonatal hypocalcemia and bone changes. We report the case of a preterm male infant who presented hypercalcemia before developing hypocalcemia after maternal magnesium sulfate therapy. Magnesium sulfate was used for premature rupture of membranes for 32 days, and the patient was delivered at 33 weeks gestation. The cord blood showed ionized calcium 1.54 mmol/L. His serum calcium and magnesium were 11.4 mg/dL and 3.5 mg/dL after birth and fell to 6.6 mg/dL and 2.7 mg/dL at 6 hours, respectively. The intact parathyroid hormone level was 18 pg/mL at 6 h. Radiography showed transverse radiolucent metaphyseal bands of the proximal humerus bone, suggesting disturbance in normal ossification. Transient hypercalcemia before the development of hypocalcemia after maternal magnesium sulfate therapy has not been previously reported. We speculate that maternal long-term magnesium sulfate therapy led to defective ossification and transient hypercalcemia in the offspring. Subsequent hypocalcemia was thought to be due to the inhibition of parathyroid hormone secretion by hypercalcemia and hypermagnesemia.

Key words: hypercalcemia, hypocalcemia, magnesium sulfate, bone change

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Introduction

Magnesium sulfate ($MgSO_4$) is a tocolytic agent used to treat preterm labor. $MgSO_4$ in women at risk for preterm delivery decreases the occurrence of cerebral palsy in the offspring (1). Neonatal hypocalcemia is well known after maternal $MgSO_4$ therapy due to the inhibition of PTH secretion by hypermagnesemia (2). Bone changes in neonates that suggest disturbance of normal ossification have also been reported after maternal $MgSO_4$ therapy (3). Therefore, the United States Food and Drug Administration recommends limited use of $MgSO_4$ (4). It is not known whether bone changes are related to neonatal hypocalcemia in this setting and if so what the mechanism involved is. In contrast, two reports of hypercalcemia after maternal $MgSO_4$ therapy were found in the literature (5, 6). However, the sequential occurrence of hypercalcemia and hypocalcemia in the same neonate has not been previously described. Here, we report the case of a preterm infant with transient hypercalcemia followed by hypocalcemia after long-term maternal administration of $MgSO_4$. Bone changes were also observed in the infant, which may suggest a mechanism of hypercalcemia after maternal $MgSO_4$ therapy.

Case Report

A 37-yr-old Japanese woman in her first pregnancy was treated for premature rupture of membrane with a drip infusion of ritodrine hydrochloride at 27 wk and one day gestation. Because she developed drug-induced exanthema at 29 wk gestation, ritodrine hydrochloride was switched to $MgSO_4$, which was used for 32 d. An initial dose of 4 g $MgSO_4$ was administered in the first 30 min, followed by a continuous infusion of 1 g/h. The total dosage of $MgSO_4$ was 825 g. The maternal serum calcium level was 7.8 mg/dL, albumin 2.9 g/dL, phosphate 5.4 mg/dL, and magnesium 4.3 mg/dL at 33 wk gestation. She delivered a male infant vaginally at 33 wk and 4 d. The infant's birth weight was 2014 g. The Apgar score was 5 and 8 at 1 and 5 min, respectively. The infant was intubated for hypotonia and respiratory distress. The cord blood showed an ionized calcium level of 1.54 mmol/L. His serum calcium level was 11.4 mg/dL, magnesium 3.5 mg/dL, albumin 3.0 g/dL, phosphorus 7.9 mg/dL, and alkaline phosphatase 416 U/L (Japan Society of Clinical Chemistry method). The urine calcium-creatinine ratio was 1.38. After 6 h, the serum calcium level was 6.6 mg/dL, ionized calcium 0.96 mmol/L, magnesium 2.7 mg/dL, albumin 2.8 g/dL, phosphorus 6.2 mg/dL, and intact PTH 18 pg/mL. The urine calcium-creatinine ratio was 0.18. We started an infusion of calcium gluconate at 30 mg/kg/d, and the calcium level was normalized. The time courses of the serum calcium and magnesium levels are shown in **Fig. 1**. A radiograph on day 0 showed transverse radiolucent metaphyseal bands of the proximal humerus and distal femurs, indicating a disturbance in ossification (**Fig. 2**). A radiograph on day 23 showed a similar finding.

Discussion

We present the case of a preterm infant with transient hypercalcemia followed by hypocalcemia after maternal $MgSO_4$ therapy. Radiography showed defective ossification, which could be due to the long duration of $MgSO_4$ infusion (32 d). The bone changes may explain the hypercalcemia, which might have contributed to the development of hypocalcemia.

Neonatal hypocalcemia is well known after maternal $MgSO_4$ therapy (2); however, two reports of hypercalcemia were found in the literature. Donovan *et al.* reported slightly elevated serum calcium levels

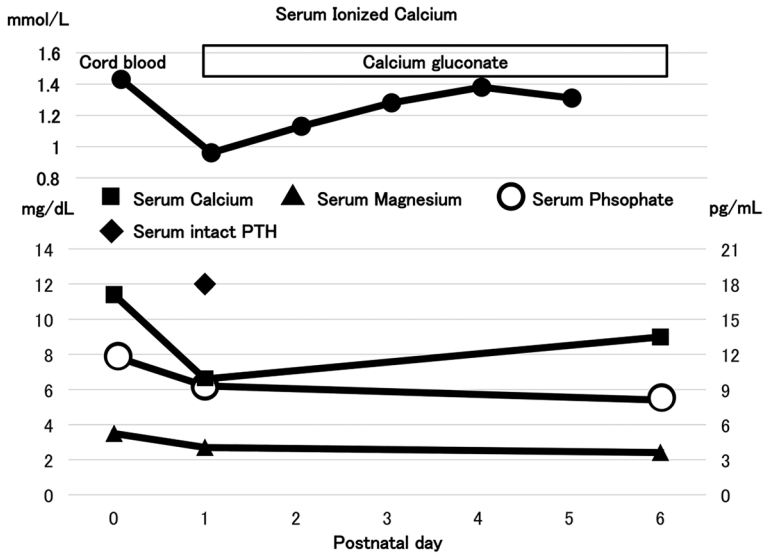

Fig. 1. Levels of ionized calcium, calcium, phosphorus, and magnesium in the cord blood and newborn's serum. Transient hypercalcemia was followed by hypocalcemia. Magnesium level normalized on day 1.

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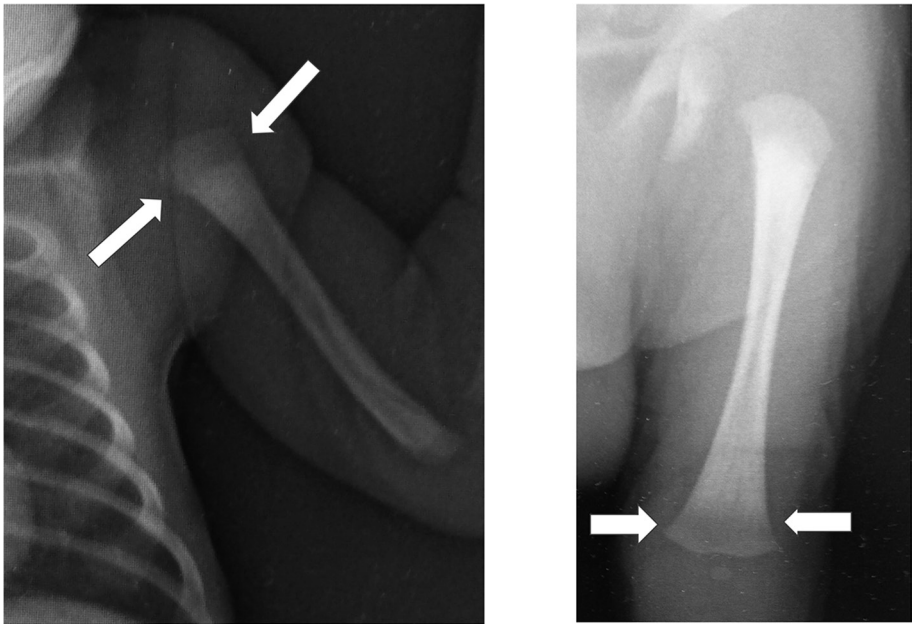

Fig. 2. Radiograph of the left proximal humerus and distal femurs on day 0. A transverse radiolucent band was observed (arrows).

in newborns of twenty pre-eclamptic mothers treated with $MgSO_4$ (5). The mean placental vein calcium level was 11 mg/dL and magnesium 4.5 mg/dL. The mean serum calcium level was normal 6 h after birth. The serum calcium level, which was monitored for 72 h after birth, remained normal. The most common reason for $MgSO_4$ administration was preeclampsia. Five infants were moderately asphyxiated (1 min Apgar score 4 to 7). The authors speculated that elevated fetal serum magnesium caused a shift of calcium from the bone to the plasma, resulting in hypercalcemia. Vahabi *et al.* also reported hypercalcemia, which was detected at birth in 9.3 percent of term infants after maternal $MgSO_4$ therapy (6). In contrast, hypercalcemia was not observed in preterm infants. The most common reason for $MgSO_4$ administration was preeclampsia. The Apgar score at 5 min was 5 to 7 in 8.2% of the subjects, and none had a score under 5. The association between Apgar scores and serum calcium levels was not investigated. Moreover, the mean duration of $MgSO_4$ therapy and the time course of serum calcium have not been described.

Matsuda *et al.* retrospectively investigated the relationship between maternal $MgSO_4$ therapy and neonatal bone abnormalities (3). Radiographic abnormalities of neonatal bone were related to early gestational age and long-term $MgSO_4$ administration. The mean duration of $MgSO_4$ use was 25.9 d. The reasons for $MgSO_4$ administration were preeclampsia, preterm labor, or both. In their study, the neonatal calcium levels were not described. Tsukahara *et al.* also reported the characteristics of neonatal bone changes in 26 infants after maternal $MgSO_4$ therapy (7). They identified three risk factors for bone abnormalities. First, the duration of $MgSO_4$ therapy exceeded 5 to 6 wk. Second, $MgSO_4$ was administered during the second trimester. The initiation of $MgSO_4$ from 22 to 26 wk led to long-term use. The third factor was multiple pregnancies. Our patient, however, had none of these risk factors. In Tsukahara's study, neonatal serum calcium levels were not measured. Yokoyama *et al.* studied 58 infants after maternal $MgSO_4$ administration of more than 5 d (2). Bone abnormalities were detected in two patients, who were twins. The duration of maternal $MgSO_4$ therapy was 38 d. $MgSO_4$ therapy was started at 26 wk and continued until cesarean section at 34 wk gestation. The mean serum calcium level in the 58 infants was 8.51 mg/dL, which was significantly lower than that of controls matched for gestational age and birth weight.

Hypocalcemia after $MgSO_4$ therapy is ascribed to the inhibition of PTH secretion by hypermagnesemia (8). Our patient's PTH level was low when hypocalcemia was detected at 6 h after birth. In a study by Rantonen *et al.*, neonatal hypermagnesemia after maternal $MgSO_4$ therapy was associated with hypercalciuria and PTH suppression (9). The authors speculated that hypercalciuric response was induced through hypermagnesemic inhibition of PTH production. In our patient, hypercalciuria was detected during hypercalcemia. Thus, serum PTH levels, although not measured, may also have been inhibited by hypercalcemia.

Hypercalcemia is known to occur in subcutaneous fat necrosis in newborns (10). It is also associated with asphyxia. In our patient, the Apgar score was 5 and 8 at 1 and 5 min, respectively, and subcutaneous nodules were not found. Other causes of neonatal hypercalcemia include maternal hypoparathyroidism. Maternal hypocalcemia is known to stimulate the fetal parathyroid glands (11). In our case, the maternal serum calcium level was at the lower end of the normal range, most

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likely due to hypermagnesemia. Therefore, maternal low normal calcemia due to $MgSO_4$ therapy may have contributed to neonatal hypercalcemia (12).

In conclusion, we report the case of a preterm infant with transient hypercalcemia followed by hypocalcemia after maternal $MgSO_4$ therapy. This clinical course has not been described previously. Concurrent bone changes may suggest that the hypercalcemia was caused by inhibited calcium deposition secondary to hypermagnesemia (**Fig. 3**). Hypercalcemia may have also contributed to the inhibition of PTH levels. To elucidate the relationships among maternal $MgSO_4$ therapy, serum calcium levels, and defective ossification, further studies are ongoing.

Conflict of Interests: The authors have declared that no conflict of interest exists.

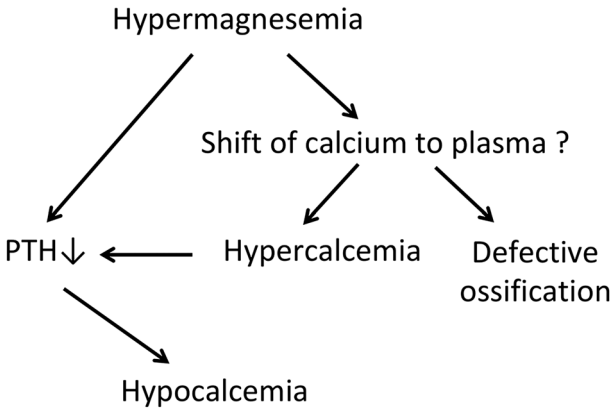

Fig. 3. Proposed mechanism of transient hypercalcemia followed by hypocalcemia and bone abnormalities in our patient.

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