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Generalized Myoclonic Seizures in a Neonate: A Rare Occurrence in Hypocalcemic Etiology Secondary to Maternal Vitamin D Deficiency

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Abstract **Case Report**

Maternal vitamin D insufficiency is not unheard of. In India, the most common cause of maternal deficiency in vitamin D and or calcium is due to the significant lack in the staple diet. Breastfeeding infants of such mothers are at an increased risk of developing vitamin D deficiency and hypocalcemia presenting with seizures. We present a case of an infant with hypocalcemic seizures secondary to vitamin D deficiency in both mother and child. The seizure activity initially tackled with an anti-epileptic and later tapered to stop after identification of hypocalcemia as the etiology through blood investigations and radiological evidence. Treatment with Calcium Gluconate was then given along with additional correction dose of Vitamin D. Upon investigation the mother was also found to have significant Vitamin D deficiency which was addressed as well. When maternal vitamin D insufficiency is the cause of neonatal hypocalcemic seizures, it may occur in both term and preterm neonates. Occurrence of generalized convulsions in the afebrile neonate represents a serious problem.

Keywords: Hypocalcemia, Convulsions, Vitamin D deficiency, Neonatal seizures.

INTRODUCTION

A seizure results from abnormal electrical activity in the brain and is a paroxysmal, time limited change in motor activity or behavior. Neonatal seizures differ considerably from seizures in older children because the newborn infant is less able to sustain generalized, epileptiform discharges. Hence seizures in a newborn are almost always subtle, in the form of lip-smacking, focal movements or isolated eye, mouth or tongue movements. Healthy term babies undergo a physiological nadir in serum calcium levels by 24-48 hours of age. This dip might be related to delayed response of parathyroid and calcitonin hormones in a newborn. Neither parathyroid nor calcitonin hormones cross the placental barrier. This early-onset hypocalcemia presents within 3 days of birth and requires short term therapy only whereas late onset hypocalcemia, as seen in this baby, presents after 7 days of birth and requires long term therapy [1].

Establishing the diagnosis in patients with hypocalcemia can be difficult. A wide range of disorders exist like hypocalcemic hypercalciuria, congenital hypoparathyroidism, infantile osteopetrosis, renal dysplasia, autoimmune polyglandular endocrinopathy, genetic disorders [2, 3]. Calcium deficiency has been implicated in some, but not all disturbances of phosphate metabolism and iron deficiency may be present [4]. Awareness of hypocalcemia as a cause of seizures is important because children are still being treated with anticonvulsants without serum calcium concentrations being evaluated.

Late-onset hypocalcemic seizures are less frequent than their counterparts, usually seen in term babies, and can present as late as by the end of 2 months after birth. The main etiological factor is hypoparathyroidism with significantly low serum PTH concentration in the presence of hypocalcemia and hyperphosphatemia. It may even be asymptomatic or present as tremors, irritability, or subtle seizures [7]. Newborns with hypomagnesemia fall into two groups: transient hypomagnesemia and chronic congenital (primary) hypomagnesemia. Both cause secondary hypocalcemia by impairing parathyroid hormone secretion and by blunting the end-organ response to parathyroid hormone [8].

We report a neonate with generalized seizures caused by severe hypocalcemia, hypomagnesemia, hyperphosphatemia and severe Vitamin D deficiency in both mother and baby.

CASE REPORT

A 7-day old male baby was admitted to neonatal intensive care unit (NICU) of a tertiary care hospital with history of recurrent episodes of Generalized myoclonic seizures in a 24-hour period manifesting as rapid movements of both upper and lower limbs with upward eye rolling and lip smacking. He was born via caesarean section (In view of failure of progression of labour) at term gestation and had a birth weight of 2.7 kg. He was exclusively breastfed since birth. His postnatal period was uneventful. The mother was poorly nourished and took vitamin supplements irregularly during pregnancy. The baby had no history of fever, trauma, or any untoward post-natal event.

Upon presentation the seizure activity was controlled at first with a stat dose of IV Midazolam. The seizure recurred after 1 hour due to which IV Phenobarbitone was started to control seizure activity. Since the seizure was Generalized myoclonic type and kept recurring frequently, a neurological focus was initially suspected, and Inborn Error of Metabolism also kept in the provisional diagnoses as a possibility. However, the neuro assessment of the baby was within normal limits. The blood glucose level was normal. Laboratory investigations in blood revealed calcium levels of 5.2 mg/dl (Normal range 8.4-10.2mg/dl), Serum Magnesium levels of 0.88 mg/dl (Normal range 1.6-2.3 mg/dl), serum Phosphorus levels of 9.21 mg/dl (Normal range 3.5-5.0 mg/dl), Vitamin D was <8.0 ng/ml (normal levels 30-100 ng /ml), Serum Parathyroid Hormone levels were 137 pg/ml (normal range 12-80 pg/ml). Radiological evaluation was done of the left hand with wrist radiograph which showed involvement of distal end of left Radius and Ulna, showing mild cupping with brush powder appearance suggestive of Stage 1 rachitic changes.

The baby was started on treatment with IV Calcium Gluconate (2ml/kg/dose-6th hourly) and continued for 3 days after which it was converted to oral supplementation (100mg/kg/day) for a 6-month course. The baby also required Magnesium correction, which was given as 0.2ml/kg in 5ml NS over 30 minutes, once daily for 3 days. Vitamin D supplementation was initiated at a dose of 1000 IU per day and continued for 6 months. Phenobarbitone was tapered to stop before discharge. As is routine, evaluation of maternal Serum Calcium and Vitamin D was subsequently done. Maternal Vitamin D levels were 8.2 ng /ml (Normal range 30-100ng/ml). She got vitamin D supplementation for next 10 weeks and was advised dietary modifications for the same.

The baby was seizure free since starting Calcium and Magnesium supplementation and did not have any further episodes till discharge. Repeat investigations were done at follow-up a month later which revealed normalization of both Calcium and Magnesium levels.

Vitamin D levels were evaluated for both mother and child at 6 months of age which was normal. The baby achieved developmental milestones within normal limits for age.

DISCUSSION

Maternal vitamin D deficiency is one of the major risk factors for neonatal vitamin D deficiency followed by neonatal hypocalcemia [7]. Hypocalcemia is recognized cause of seizure in neonate and infants [8].

While hypoxic ischemic encephalopathy and metabolic causes like hypoglycemia, early-onset hypocalcemia dominate the etiology behind seizures within 24 hours of life, Infections are the most common cause of neonatal seizures in the late first week and during the second week of life. Seizures caused by inherited metabolic disorders present any time in the neonatal period and infancy. Intractable seizures unresponsive to usual therapy may result from a congenital pyridoxine deficiency which is a relatively late onset cause of seizures, may respond to vitamin B-6 replacement and is a diagnosis of exclusion [9].

Generalized myoclonic seizures in a neonate is the rarest among the seizure types with an incidence of less than 20% [15]. The differential diagnosis of generalized seizures can be narrowed down, to a limited extent, to Intraventricular hemorrhage, Epileptic syndromes or Inborn Errors of Metabolism. Late-onset hypocalcemic seizures with hypomagnesemia and Vitamin D deficiency in both mother and baby together forms a rare occurrence. The rarity of generalized seizures in infants younger than 2 years is thought to be related to the relative immaturity and lack of organization of their developing brain, characterized by variable neuronal excitability, imperfect myelination, and incomplete interhemispheric connections [14].

Calcium plays a key role in many functions in the body and is a crucial cofactor in muscle contraction. Blood calcium concentration is not entirely dependent on dietary intake and despite variations, is controlled within precise limits. It is regulated principally by three hormones: Parathyroid hormone, Calcitonin and 1, 25-dihydroxycholecalciferol. Major causes which affect calcium homeostasis are low maternal vitamin D stores, cow's milk feeding, physical sunscreen agents, malabsorption (celiac disease, pancreatic insufficiency, cystic fibrosis, biliary obstruction), decreased synthesis or increased degradation of 25(OH)D (chronic liver disease), and drugs[5]. Lower maternal educational

status and large family size are socio-economic factors playing an important role in maintaining calcium homeostasis [6].

Existence of a hyperthyroid state is normal in the pregnant mother. As evidenced by higher levels of calcium and phosphorus in cord blood compared with maternal blood, Calcium and inorganic phosphorus are transferred across the placenta against a concentration gradient. Neither parathyroid hormone nor calcitonin crosses the placenta. In the fetus, serum calcium levels are comparable with those seen in older children and adults. In normal, healthy newborns this gradually decreases after birth to a level that is lower than that found in older infants and children at 2 to 3 days of age, and then slowly returns to normal adult level by 5 to 10 days of age. The decline in the calcium in the newborn period is greater in infants who are not fed or who receive cow's milk than in breast-fed infants, and greatest in infants who are premature, asphyxiated, and have a diabetic mother [10]. Serum parathyroid hormone levels are low at birth, and gradually increase over the first 48 hours to normal levels in response to the decrease in serum calcium level. At the same time serum calcitonin levels increase sharply to a peak at 12 to 24 hours of life, and then slowly decrease over the next week to level off at concentrations above adult normal [11]. Infants are able to convert vitamin D to 25-hydroxy vitamin D and 1, 25-dihydroxy vitamin D (calcitrol) in normal fashion at birth [12].

Transplacental transport of vitamin D, mostly 25-D, typically provides enough vitamin D for the first 2 month of life unless there is severe maternal vitamin D deficiency [9]. It is quite common to find vitamin D insufficiency in otherwise, healthy pregnant women [10]. Infants born to such mothers have reduced umbilical cord blood concentrations of 25-hydroxycholecalciferol [11]. In addition, breast milk contains only 12-60 IU of vitamin D per litre. This varies according to maternal vitamin D status [12]. Intestinal calcium absorption doubles in the first trimester, well before the rise in free calcitriol levels during the third trimester. Neonatal hypocalcemia can occur in infants born of mothers with severe vitamin D deficiency, but it is in the weeks to months after birth as intestinal calcium absorption becomes more dependent on calcitriol. Vitamin D deficiency most commonly occurs in infancy because of a combination of poor intake and inadequate sun exposure and usually present with rickets.

The most important causes of neonatal vitamin D deficiency include maternal vitamin D deficiency, renal insufficiency, malabsorption, and hepatobiliary disease. As the index neonate had normal renal function, liver function tests along with normal renal architecture and hepatobiliary tree in abdominal ultrasonography, renal and hepatobiliary causes for hypovitaminosis D were ruled out. There were no features of malabsorption in the neonate. As mother's vitamin D levels were low, maternal vitamin D deficiency was attributed to the neonatal hypovitaminosis D and symptomatic late onset neonatal hypocalcemia.

Chacham S *et al*. [13] also presented a case of neonate with hypocalcemic seizures but those were not of the Generalized myoclonic type.

CONCLUSION

In conclusion, generalized convulsions in the afebrile neonate represent a serious and etiopathogenically very heterogeneous problem. Extremely rare, as in the case of our patient, is the occurrence of Generalized myoclonic seizures with a background of hypocalcemia. We report a term male neonate with symptomatic late onset neonatal hypocalcemia due to vitamin D deficiency and maternal hypovitaminosis D. There was clinical and biochemical response to calcium and vitamin D supplementation. Follow-up at 6 months revealed no abnormalities and the baby was doing fine in terms of both physical and neurological development. The particular challenge of interpreting neonatal seizures may require concurrent EEG analysis to be certain of the true nature of the ictal event and to aid in its classification. Instead, and particularly in the refractory patient population, video-EEG monitoring may be helpful in better characterizing the disorder.

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