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Case Report

Severe neonatal hypercalcemia secondary to Aluminium toxicity

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ABSTRACT

Aluminum, the most abundant metal on the planet, though inert can lead to toxicity when repeatedly exposed. Infants mainly get exposed to aluminum via formula milk whereas NICU babies are exposed to it through parenteral nutrition. Moreover, in pre-term babies with feed intolerance, when added with aluminum containing antacids develop abnormal accumulation of aluminum. Aluminum toxicity inadvertently leads to hypophosphatemia, metabolic bone diseases with occasional hypercalcemia as well as many other systemic involvements in the form of encephalopathy, dementia and microcytic anaemia. With stoppage of oral antacid, transition from parenteral nutrition to enteral feeds and supplementation of phosphate, causes gradual resolution of toxicity over a period of time.

Keywords: Antacids, Aluminium toxicity, Hypercalcemia, Preterm neonates

INTRODUCTION

Aluminium is the most abundant metal on earth and is well known to cause human toxicity.[1] Humans can get exposed through drinking water, cans, cooking utensils, medicines, antiperspirants. In past, dialysate in tap water was also a source of aluminium toxicity when used in dialysis.

Infants mainly get exposed to aluminium thorough formula milk; both lactose and soya based and aluminium containing oral antacids.[2] NICU babies are exposed to it through parenteral nutrition.[3] FDA has recommended that aluminium in parenteral nutrition should be <25 meq/Lit. Albumin solution and calcium gluconate solution in glass vials are also some of the sources.[4]

Aluminium gets excreted mainly by the kidneys. Therefore, neonates with renal insufficiency are at risk for abnormal accumulation and toxicity. Uremic children treated with aluminium-containing antacids has shown toxic accumulation of aluminium.[5] Aluminium toxicity presents with encephalopathy, dementia, hypophosphatemia and hypercalcemia and sometimes, microcytic anaemia.[6] We are presenting a case where a 34-day old growing preterm presented with severe hypercalcemia and origin of it could be traced back to antacids.

CASE REPORT

28.3 weeks preterm ELBW female baby, birth weight 920 gm was born to a 26-year-old primi by emergency LSCS in view of PPROM with non-progression of labor. For her respiratory distress she was managed with non-invasive ventilation and surfactant as per standard protocol. Baby was initially started on total parenteral nutrition. Because of non-availability of phosphorus solution for a short period, phosphate supplementation could not be done in the parenteral solution. She had multiple episodes of feed intolerance for which head end elevated position, pantoprazole as proton pump inhibitor, metoclopramide as prokinetic drug and aluminium hydroxide dry gel were tried.

On day 34, baby had recurrent episodes of apnoea along with generalised floppiness. She required non-invasive respiratory support for subsequent 10 days. Baby had no

signs of metabolic bone disease. Investigations for apnoea were normal apart from alarmingly high level of serum calcium. Further investigations revealed: Total serum calcium: 16.27 (8.5-10.6) mg/dL; ionized calcium: 3.8 (4.2-5.9) mg/dL; Serum phosphate: 0.45 (7.6±1.1) mg/dL; Serum Mg: 2.1 (1.8-2.5) mg/dL; iPTH (1-84 - 0.68 (1.6 - 6.9) p mol/L by CMIA method[; 25 (OH) D-8 (30.01-100) ng/mL by CMIA method; Serum alkaline phosphatase: 586 (48-406) U/L; urine calcium/creatinine 3 (<2.4); undetectable urine phosphorus; total protein-4.5 (4.1-6.3) g/ dL and serum albumin: 3.8 (3.7-5.4) g/dL.[7-8] Further her blood gas was within normal limits. USG KUB region didn't show any evidence of nephrocalcinosis. Mother had serum calcium -9.5 mg/dL, serum phosphorus- 3.1 mg/dL, 25(OH)D-15.6 ng/mL, alkaline phosphatase-325 U/L, iPTH-6.4pmol/L. Appreciating severe hypercalcemia, normal saline fluid boluses and frusemide induced forced diuresis was started. Total serum calcium returned to normal level after 48 hours of forced saline diuresis. Considering the possibility of aluminium hydroxide gel causing elevated plasma aluminium level and resulting hypercalcemia, serum aluminium level was investigated. It was 89.2 mcg/L (>50 is toxicity range).

Oral phosphate supplementation was given at 1 mmol/kg/day in 4 divided doses after stoppage of oral antacid. Vitamin D supplementation was also started. Baby started tolerating feeds gradually and was on multicomponent fortified expressed breast milk. With stoppage of aluminium exposure, normalization of serum aluminium (<30 mcg/L) was seen over next few weeks.

DISCUSSION

Severe hypercalcemia (16.27 mg/dl) in a growing preterm baby entails: (i) phosphorus free TPN in VLBW infants, (ii) neonatal hyperparathyroidism, (iii) familial hypocalciuric hypercalcemia or (iv) high serum aluminium secondary to consumption of aluminium hydroxide gel.

Possibility of osteopenia of prematurity and hypervitaminosis D was ruled out as low phosphorus level in a growing preterm neonate suggested osteopenia of prematurity (may be associated with hypercalcemia), but it is associated with normal PTH level. Similarly, vitamin D was in deficiency range in our case. In the presence of hypercalcaemia, a clearly elevated PTH of >7.0 pmol/L is diagnostic of primary hyperparathyroidism, while an appropriately suppressed result of <2.6 pmol/L virtually excludes primary hyper-parathyroidism. Normal Uca/ Ucr ratio excluded neonatal familial hypocalciuric hypercalcemia.

In NICU setting, hypercalcemia usually results from inadequate provision of phosphorus, as with use of low or no phosphorus in TPN in VLBW infants. Hypercalcemia is more likely if there is concomitant use of calcium supplements.

The baby in the present case consumed around 120 mg/kg/day of elemental aluminium for a period of 2.2 weeks. Aluminium hydroxide gel in the antacid caused raised aluminium level, which was further contributed by parenteral nutrition.[3] Tsou, et al studied 10 infants, who had consumed antacids for at least 1 week, while 16 infants without receiving antacids acted as control population.[5] Plasma aluminium level (37.2±7.13 µg/L) in the study group was significantly higher than that of the control group (4.13±0.66 µg/L) (P <0.005). Authors concluded that in infants with normal renal function who are consuming high doses of aluminium-containing antacids can have high plasma aluminium level.

Rodriguez et al, evaluated the effect of an intravenous aluminium infusion on total and ionized calcium in rats.[9] Intravenous aluminium increase total plasma calcium and decrease ionized calcium. The mechanism he proposed, also supported by in vitro data, is increased binding of calcium in the plasma which decreases ionized calcium. As a result of the decreased concentration of ionized calcium, movement of bone and interstitial calcium into the vascular space may occur, thus increasing total plasma calcium. Raised total calcium and low ionic calcium pointed towards aluminium toxicity in the present case.

Hypophosphatemia can be explained by aluminium inhibiting phosphate absorption from gastro-intestinal tract and is compounded by no phosphate supplement in parenteral nutrition solution. Haglin et al demonstrated this fact that hypophosphatemia can be induced by dietary aluminium hydroxide.[10]

CONCLUSION

The safety of antacids containing aluminium in NICU is arguable. Even its use for a short period can raise aluminium level in neonates. They should be used judiciously, with careful monitoring of the cumulative doses of aluminium and plasma aluminium level.

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