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Case Report

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Neonatal hypercalcaemia associated with congenital adrenal hyperplasia

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ABSTRACT

Adrenal insufficiency is an important and potentially life-threatening condition, and it is also a rare cause of hypercalcaemia. We report a case of resistant hypercalcaemia (calcium [Ca] 13.8 mg/dL) in an 18-day-old male infant in which normalised serum Ca levels could not be achieved even after treatment with hyperhydration and furosemide. Long term lowering of serum Ca was only achieved after the diagnosis of congenital adrenal hyperplasia (CAH) was made and the initiation of hydrocortisone replacement therapy. Prior to presentation, the patient had only mild scrotal hyperpigmentation, and findings were otherwise unremarkable for CAH. Hypercalcaemia is a rare but well-recognised complication of CAH. The mechanism of this form of hypercalcaemia is unclear, because congenital adrenal insufficiency is a rare cause of hypercalcaemia and patients are treated as soon as the diagnosis is made. Neonatologists should consider CAH in the differential diagnosis of neonatal hypercalcaemia.

1.Introduction

Adrenal insufficiency is an important and potentially life-threatening condition, and is also a rare cause of hypercalcaemia. It was first described in 1932 by Loeb (Loeb, 1932), in an adult patient with Addison's disease. In the majority of published cases, patients with hypercalcaemia and adrenal insufficiency present in adulthood (Walser et al.,1963; Pieters et al., 1990; Diamond and Thornley, 1994; Bhatti and Flynn 2012). However, there is a single case report of a 12 year old who presented with the hypercalcaemic effects of adrenal insufficiency due to idiopathic atrophy of the adrenal glands (Prader et al.,1959). Herein, we report a case of congenital adrenal hyperplasia (CAH) due to 11-beta-hydroxylase deficiency in a new-born presenting with hypercalcaemia.

2.CaseReport

An 18-day-old male infant was born at 36 weeks gestation to a 30-year-old healthy mother by emergency caesarean section for foetal distress and intrauterine growth retardation. His parents were first-degree cousins. At birth the patient weighed 2200 g with a length and head circumference of 46 and 34 cm, respectively. The patient was referred to our paediatric endocrinology clinic due to his resistant hypercalcaemia.

On physical examination, the infant was ill appearing with the following vital signs: heart rate 160 beats/min, respiration rate 68/breaths/min and blood pressure 93/67 mm/Hg (>95th percentile). Genital examination revealed bilateral palpable gonads, a 3.5-cm phallus and mild scrotal hyperpigmentation. The laboratory evaluation revealed the following results: glucose 58 mg/dL; creatinine (Cr) 0.7 mg/dL; calcium (Ca) 13.8 mg/dL; phosphorus (P) 6 mg/dL; sodium 134 mEq/L; potassium 6.8 mEq/L; alkaline phosphatase 1100 U/L; adrenocorticotropic hormone (ACTH) 104 pg/mL (normal range [N]:6-48); morning (8am) cortisol 3.4 µg/dL (N:4-21); 17-hydroxyprogesterone (17-OHP) 1900 ng/dL (N:<2000); dehydroepiandrosterone sulphate (DHEA-S) 1000 µg/dL; total testosterone 506 ng/dL (N:75-400); progesterone 4.05 ng/mL; androstenedione 3.4 ng/mL (N:0.1-0.5); free T4 1.46 ng/dl (N: 0.93-1.7); and TSH 2.7 uIU/mL (N: 0.5-4.2). During a standard-dose ACTH test (Synachten® 0.25 mg) the peak cortisol level was 12 µg/dL, and the peak 17-OHP and 11-deoxycortisol levels were 4800 ng/dL and 37.1 ng/mL, respectively. T treatment with intravenous (IV) he diagnosis of 11-beta-hydroxylase deficiency was established. Further evaluation revealed a serum 25-OH vitamin D level of 10.5 ng/mL and a parathyroid (PTH) level of 4.8 pg/mL. Laboratory evaluation of both parents indicated that their serum Ca, P and PTH levels, as well as their urine Ca/Cr ratio, were all normal. Abdominal ultrasonogram of the patient demonstrated medullary nephrocalcinosis. Interestingly, the patient's serum Ca levels did not normalise after

saline followed by IV furosemide at a dose of 1 mg/kg every 12 h. Oral hydrocortisone treatment at a dose of 20 mg/m2/day was commenced. Hypertension and hypercalcaemia were corrected after 3 days of hydrocortisone replacement therapy. The patient's serum Ca level decreased to 9.1 mg/dL, with a corresponding random urine Ca/Cr ratio of 0.1, and the values remained consistent (Figure 1). During a follow-up appointment, the patient had no evidence of hypercalcaemia or hypertension.

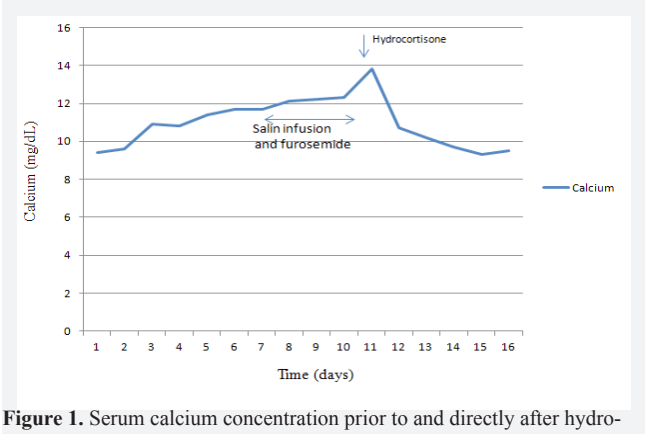

Figure 1. Serum calcium concentration prior to and directly after hydrocortisone replacement therapy.

3. Discussion

The common causes of hypercalcaemia in infants are primary hyperparathyroidism, idiopathic infantile hypercalcaemia, drugs (e.g. thiazide diuretics and vitamin A) and hypophosphatemia. Hypercalcaemia has also been reported in infants given human milk with a very high vitamin D content due to maternal hypoparathyroid treatment with high-dose vitamin D, infants who receive milk with excessive vitamin D fortification due to a processing error, and preterm infants given chronic vitamin D supplementation with a high-Ca and high-P milk formula. Neonates with extensive subcutaneous fat necrosis often have a history of perinatal asphyxia and may develop hypercalcaemia after a period of low or normal serum Ca concentration (Lietman et al.,2010). The data from our patient provide no evidence of primary hyperparathyroidism, because the PTH-vitamin D axis was suppressed. In our patient, there was no history of drug use or vitamin D3 supplementation. Additionally, there was no evidence of excessive maternal use of vitamin D3 or other drugs. Maternal laboratory tests, including Ca, PTH, vitamin D, thyroid function and urinary Ca excretion, were normal. Finally, the patient did not have any of the dysmorphic features of Williams syndrome or the typical skin changes indicating subcutaneous fat necrosis. When an extensive work up excluded the most frequent causes of hypercalcaemia, the patient's hypercalcaemia was attributed to adrenal insufficiency. Adrenal insufficiency is a rare cause of hypercalcaemia and physiological amounts of glucocorticoids may normalise serum Ca levels. Hypercalcaemia has been reported to occur both with primary adrenal insufficiency and secondary adrenal failure (Downie et al.,1977; Miell et al. 1991; Vasikaran et al.,1994; Patel and Clayton, 1994). In the present case, the examination and laboratory work-up excluded the most frequent causes of hypercalcaemia.

The hypercalcaemia observed in our patient was finally attributed to an 11-beta-hydroxylase deficiency, the second most common cause of CAH characterised by adrenal insufficien cy and virilisation of external genitalia, due to the normalisation of the patient's blood pressure following hydrocortisone therapy. Multiple mechanisms for hypercalcaemia have been proposed. It has been suggested that hypovolaemia and a decreased glomerular filtration rate lead to a reduction in Ca filtrate and increased proximal tubular reabsorption of Ca and sodium (Muls et al.,1982; Vasikaran et al.,1994).

These alterations in renal function are secondary to volume depletion and should improve rapidly following rehydration. In the case presented here, urine Ca excretion was increased indicating an increased amount of Ca in the extracellular fluid. Therefore, fluid infusion and furosemide treatment could not fully correct the hypercalcaemia, which persisted irrespective of volume status or glomerular filtration rate indicating the low significance of renal factors in this case. In contrast, complete correction of plasma Ca levels was observed shortly after the initiation of glucocorticoid replacement therapy. Another potential cause of hypercalcaemia is increased bone resorption of Ca. Physiological amounts of glucocorticoids are essential for the preserve of bone structure (Muls et al.,1982). The mechanism by which glucocorticoid deficiency enhances Ca release from bone was described by Montoli et al. (Montoli et al., 1992). The authors found no evidence of increased osteoclastic activity in bone biopsies from patients with Addison's disease, and all cellular activities at the trabecular surfaces appeared to be depressed. Thus, Ca mobilisation from bone was not associated with bone remodelling. Moreover, glucocorticoids appear to play an important role in modulating the metabolism of PTH and its influence on Ca homeostasis (Lee et al., 1978). The levels of PTH and 25-OH vitamin D were low in our patient, indicating a suppressed PTH-vitamin D axis, and these levels returned to normal after corticosteroid replacement therapy similar to previous reports (Muls et al.,1982; Montoli et al., 1992).

In addition, excessive intestinal absorption of Ca has been suggested as a potential cause of the type of hypercalcaemia observed in our patient (Muls et al.,1982). However, since our patient had very poor intake of his mother's milk, intestinal absorption was excluded as a significant source of Ca. While examining the effects of a Ca rich diet, Walser et al. (Walser et al.,1963) demonstrated that hypercalcaemia occurred with comparable frequency in adrenalectomised dogs fed a Ca-rich or Ca-free diet. Overall, these findings indicate that in our patient, the aetiology of hypercalcaemia is likely increased release from bone rather than increased intestinal absorption or decreased renal excretion of Ca. In conclusion, this case report confirms that, though rare, CAH and adrenal insufficiency should be considered in cases of hypercalcaemia that can be corrected by corticosteroid administration. The patient reported herein presented with only mild scrotal hyperpigmentation and no other findings remarkable for CAH. The mechanism of hypercalcaemia in CAH patients is unclear, because congenital adrenal insufficiency is a rare cause of hypercalcaemia and patients are treated as soon as the diagnosis is made.

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