CASE REPORT

Hypoglycemia due to 3β-Hydroxysteroid Dehydrogenase type II Deficiency in a Newborn

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Background: 3β-hydroxysteroid dehydrogenase type II deficiency results in decreased production of all three groups of adrenal steroids. Recurrent hypoglycemia as a presenting feature of this disorder has not been reported earlier. **Case characteristics**: A genotypically and phenotypically normal female newborn delivered by in-vitro fertilization presenting with recurrent hypoglycemia. Primary adrenal insufficiency with insignificant mineralocorticoid deficiency and slightly elevated levels of 17-hydro-xyprogesterone, dehydroepian-drosterone sulphate and testosterone. **Outcome**: Successfully managed only with corticosteroid replacement. **Message**: Congenital adrenal hyperplasia can rarely cause recurrent hypoglycemia in newborns.

Keywords: *Corticosteroids, Hypoglycemia, Primary adrenal insufficiency.*

3-beta-hydroxysteroid dehydrogenase type II (3βHSD2) is required for the synthesis of all three groups of adrenal steroids: mineralocorticoids, glucocorticoids, and sex steroids [1]. It catalyzes the conversion of pregnenolone to progesterone (mineralocorticoid pathway), 17-alpha-hydroxypre-gnenolone to 17-alpha-hydroxyprogesterone (glucocorticoid pathway), and dehydroepiandrosterone to androstenedione (sex steroid pathway); its complete absence impairs production of all steroids [1]. It was first described in male infants with ambiguous genitalia and severe salt wasting, but can also occur in female infants who may be phenotypically normal or may have mild clitoromegaly [2,3]. Its presentation with recurrent hypoglycemia has not been reported in literature.

We herein report a female baby born to an elderly primigravida by *in vitro* fertilization (IVF) who had recurrent episodes of hypoglycemia, subsequently diagnosed with this conidition.

CASE REPORT

A 15-day-old preterm, low birth weight (1.75 kg) female infant born out of non-consanguineous parentage by cesarean section was admitted to our Neonatal Care Unit with history of poor feeding, lethargy and inadequate weight gain since 8 days. The mother was an elderly primi-gravida (48 years) with primary infertility; conception was by *in vitro* fertilization with an uneventful antenatal period. On admission, the baby was irritable with depressed reflexes and activity, had a cachectic look with no weight gain (1.75 kg), flat anterior fontanelle, stable vitals including normal blood pressure (BP 74/48 mmHg), significant hepatosplenomegaly, no abnormal pigmentation and normal genitalia. After initial stabilization, capillary blood glucose was found to be 15 mg/dL. After sending appropriate samples, treatment was started with antibiotics (injection piperacillin-tazobactum and injection amikacin) and glucose infusion rate (GIR) of 6 mg/kg/min after giving 10% dextrose bolus considering it to be a case of late onset neonatal sepsis with hypoglycemia. Sepsis screen was positive (total leucocyte count 3600/µl, absolute neutrophil count 1728/µl, immature to total neutrophil ratio 0.18, C-reactive protein 26 mg/L) while blood glucose level was 18 mg/100 mL. Other reports (urea, creatinine, liver function test) were normal except borderline low serum sodium (128 mEq/L) and slightly high serum potassium (5.8 mEq/L). CSF study and blood culture were normal. GIR was gradually increased to 10 mg/kg/minute to counter persistent hypoglycemia and the baby improved clinically. GIR was tapered after 24 hours of normoglycemia on day 4 of admission and maintained at a minimum rate of 4 mg/kg/min to avoid hypo-glycemia. Antibiotic was changed to (injection colistin sulphate) after sending another blood sample for sepsis screen and culture. Arterial blood gas analysis showed mild hyperkalemic metabolic alkalosis, and urinanalysis for non-glucose reducing substance was negative. Sepsis screen was now normal and the baby showed clinical improvement and normalization of blood glucose levels.

To investigate recurrent hypoglycemia, serum cortisol, growth hormone (GH), free T4, free T3 and TSH were assayed. Serum insulin and C peptide were estimated during a hypoglycemic episode. Serum cortisol

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level was low (2.4 mcg/dL, reference: 3.7-19.4 mcg/dL), GH was normal (24.94 ng/mL, reference: 5-40 ng/mL), and Insulin (<1.0 microU/mL, reference: 2.6-24.9 microU/mL) and C-peptide (0.221 ng/mL, reference: 0.4 -2.2 ng/mL) were low. TSH (1.60µU/mL, reference: 1.36 -8.80 uU/mL), FT_3 (2.70 pg/mL, reference: 2.70-6.40 pg/mL) and FT_4 levels (1.50 ng/dL, reference: 1.10- 2.00 ng/dL) were normal. Subsequently 8 AM plasma Adrenocorticotropic hormone (ACTH) was assayed and found to be elevated (183.9 pg/mL, reference: 7.2-63.3 pg/mL) denoting primary adrenal insufficiency.

Oral hydrocortisone was started (25 mg/m^2/day) in two divided doses whenceforth the baby remained euglycemic even after stopping glucose infusion. Since congenital adrenal hyperplasia (CAH) is the commonest cause of primary adrenal insufficiency in children [4,5], serum 17-hydroxyprogesterone [17(OH)P], dehydroepiandrosterone sulphate (DHEA-S) and testosterone levels were measured. 17(OH)P (11.8 ng/mL, reference: 0.4-2.00 ng/mL), DHEA-S (191.8 mcg/dL, reference: 3.4 -123.6 mcg/dL) and serum testosterone (71.7 ng/dL, reference: 10-25 ng/dL) were slightly elevated. CT scan of abdomen showed normal adrenals and mullerian structures while karyotyping showed 46, XX.

These biochemical findings suggest 3β-hydroxysteroid dehydrogenase type II deficiency. Estimation of 17β-hydroxy pregnenolone and dehydroepiandrosterone with genotype studies could not be done. The baby was discharged on day 45 of life with lowest effective dose of oral hydrocortisone.

DISCUSSION

3β-HSD type II enzyme deficiency is a rare autosomal recessive disorder of steroid biosynthesis resulting in increased pregnenolone, 17-alpha-hydroxypregnenolone, and DHEA and adrenal insufficiency due to decreased cortisol and aldosterone [1]. Decreased mineralocorticoid secretion in 3β-HSD deficiency results in varying degrees of salt wasting in both sexes and deficient androgen production causes ambiguous genitalia in males [6,7]. Affected females appear normal or may have mild-to-moderate clitoromegaly due to direct androgen effects of elevated DHEA and peripheral type I 3β-HSD isoenzyme mediated conversion of excess DHEA to testosterone [8]. Peripheral conversion may also result in slight elevated levels of 17(OH) P.

An elevated plasma ACTH with a low serum cortisol established the diagnosis of primary adrenal insufficiency in the infant. Absence of virilization and only slightly elevated levels of 17(OH)P excludes 21-hydroxylase deficiency while normal BP, pattern of electrolyte change and absence of virilization excludes 11 β-hydroxylase deficiency [9,10].

Episodes of hypoglycemia in the present case can be explained by low cortisol level (glucocorticoid deficiency) which was aggravated due to sepsis. Hypoglycemia induced a negative feedback mechanism causing low serum insulin and low C-peptide levels. Mild hyponatremia and hyperkalemia, which subsequently normalized with normal BP suggests insignificant mineralocorticoid deficiency.Slightly elevated levels of 17(OH) P and testosterone level were due to the peripheral conversion by 3âHSD1 enzyme.

We conclude that in a newborn presenting with recurrent episodes of hypoglycemia, CAH could be a possibility even if there is no pigmentation, virilization or overt feature of adrenal crisis.

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