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Case Report: A Rare Form of Congenital Adrenal Hyperplasia (CAH)

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Abstract

We present two cases of CAH who presented within the same time to our neonatal unit. Both cases had antenatal diagnosis of intrauterine growth restriction (IUGR) and were both born prematurely with very low birth weights. Both cases presented before the age of two months. The first case was diagnosed after developing hyponatremia and hyperkalaemia. However; both cases shared a remarkable increase in skin hyperpigmentation which was obvious to both of their mothers who had fair skin colour. These cases turned to be cases of lipoid CAH. We present these cases to highlight the importance of the antenatal diagnosis of IUGR in metabolic diseases. The presence of dark colour of the skin in fair coloured families should alert the physician to seek the diagnosis of CAH early. We think that clinicians should be aware of the presence of such diagnostic clues to establish an early diagnosis in order to avoid further morbidities and mortalities.

Keywords: Adrenocorticotrophic Hormone (ACTH); Congenital Adrenal hyperplasia (CAH); Intrauterine Growth restriction (IUGR); Steroidogenic Acute Regulatory Protein (StAR)

Introduction

Lipoid CAH is a rare disorder of steroid biosynthesis and is considered to be the most severe form of CAH. In lipoid CAH the synthesis of glucocorticoid, mineralocorticoid and sex steroids is impaired resulting in severe adrenal failure with severe salt wasting and hyperpigmentation. Lipoid CAH can be lethal if it presents early after birth. Presence of IUGR, electrolytes imbalance and dark skin colour should raise the suspicion of the condition and the relevant investigations should be carried out to establish an early diagnosis.

Clinical Presentation

The first case presented at age of 25 days. This was a female preterm baby born at 35 weeks gestation with a very low birth of 1350 grams. Pregnancy was complicated by IUGR and oligohydramnios. At the time of presentation, the baby had hyponatremia, hyperkalaemia with normal blood glucose and normal blood pressure. The mother was concerned about the dark skin colour of the baby compared to her fair skin colour.

The second baby presented few weeks after the first baby. This was term 37 weeks gestation female baby with a low birth weight of 1550 grams. Pregnancy was complicated by IUGR. This baby also had striking dark skin colour compared to her mother. There was no evidence of electrolytes disturbances, no hypoglycaemia and no hypotension.

The electrolyte imbalance in the first baby was suggestive of CAH but the fact that both babies had such striking hyperpigmentation made us to think seriously about CAH in the second baby.

Investigations and Results

The investigations confirmed the diagnosis of CAH with super high value of adrenocortical hormone (ACTH) and very low values of cortisol, aldosterone and sex hormones. (Table). These values were consistent with severe CAH and immediate treatment was established with glucocorticoid and mineralocorticoid hormones replacement therapy. Although both babies improved clinically and biochemically, they both expired suddenly one month after starting the treatment. At the time of death there was no evidence of acute adrenal crisis.

Test	Result	Reference Range
ACTH	>2000 pg/ml	7.2- 63.3
Cortisol	1.5 nmol/L	171- 536
Aldosterone	<4.0 ng/dl	17- 154
17 Hydroxyprogesterone	<40 ng/dl	>630 (Pre-term)
Dehydroepiandrosterone	0.1 pmol/L	2.93- 16.5
Dihydrotestosterone	50 pg/ml	<50
TSH	14 mIU	0.27 – 4.2
Free T4	13.8 pmol/L	12 - 22
Tandem MS	Normal	
TORCH Serology	Negative	
Whole Exome sequence	No pathogenic Variant	
Chromosomal Karyotype	46 XY	

Table: Investigations Results

Discussion

Our two babies shared the presentation of IUGR, low birth weight, dark skin colour, female phenotype, positive consanguinity and enlarged adrenal gland on ultrasound examination. The super high ACTH value with extremely low values of cortisol, aldosterone and gonadotrophic hormones were indicative of the diagnosis of lipoid CAH. The hyperpigmentation of the skin is explained by the stimulation of the melanocytes by the high ACTH. The whole exome sequence did not reveal any pathogenic variant in both babies. Lipoid CAH is a rare disorder of steroid hormones biosynthesis and is considered to be the most severe form of CAH. It is inherited as an autosomal recessive disorder. Although most of the cases have been reported from Japan and Korea, some cases have recently been reported from the Middle East and Saudi Arabia (Kim, 2014; Subki et al., 2022).

In lipoid CAH the synthesis of glucocorticoids, mineralocorticoids and sex hormones is impaired resulting in severe adrenal failure with salt wasting and hyperpigmentation. Although there are reports of improved survival with replacement therapy, lipoid CAH is usually lethal if it presents in the first few months of life.

Two forms of lipoid CAH have been described (Hashemipour et al., 2012).The first is the classical form which occurs early in life and is life threatening. In this form babies develop female external genitalia in both human karyotypes and is mostly caused by mutations in the steroidogenic acute regulatory protein (StAR) gene.

The second form is the non-classical form which presents as late-onset adrenal insufficiency and is associated with mild or minimally disturbed sexual development (Lin et al., 1995; Bens et al., 2010).

To understand the pathophysiological changes in lipoid CAH it is important to recognize the biochemical pathways of steroid hormone biosynthesis. Steroid hormones are synthesized from cholesterol which is derived from lipoprotein-derived cholesterol esters and hydrolysis of cholesterol esters in lipid droplets (Manna et al., 2016). The first step in steroid biosynthesis is mobilization of cholesterol from the cellular stores to the mitochondrial inner membrane. In the mitochondria a dynamic protein complex is involved in the next step of steroidogenesis. The most important of this protein complex is the steroidogenic acute regulatory protein (StAR) which regulates steroid biosynthesis in steroidogenic tissues. StAR protein mediates the intramitochondrial transport of cholesterol to the site of cytochrome P450 scc which is the cholesterol cleavage enzyme. This cleavage enzyme called CYP11A1, converts cholesterol in the inner mitochondria to pregnenolone (Stocco, 2001). Pregnenolone exits the mitochondria and thereafter converted to various steroid hormones in various tissues. Steroid hormones steroidogenic enzymes are expressed in the testes, adrenals and ovaries. Production of steroid hormones in the testes and adrenals start early in fetal life. However; the ovaries do not produce steroid hormones until the start of puberty (Manna et al., 2016).

Lipoid CAH is characterized by an inborn error of steroid hormone biosynthesis resulting in almost complete inability of the newborn to synthesize steroids. Mutations in the StAR gene render it non-functional and inactive. This is the most common cause of lipoid CAH in early life. The remaining cases of lipoid CAH are accounted for by mutations in the cholesterol cleavage enzyme ((P450 scc) (Miller & Auchus, 2011; King et al., 2011). Babies with lipoid CAH are phenotypically females irrespective of the chromosomal sex. This is due to the absence of testosterone synthesis between 6 and 12 weeks of fetal life. When lipoid CAH occurs early, the adrenals are large and contain cholesterol esters (Miller & Auchus, 2011).

One of the important aspects of our two cases is the association with IUGR. It is of vital importance to consider the diagnosis of metabolic disorders in cases of IUGR given the fact that some of these cases are treatable. In fact, fetal growth has been found to depend on various hormones including insulin, thyroid hormones, adrenal hormones and pituitary hormones (Sharma et al., 2016). It is well established that fetal glucocorticoid hormones play an important role in the development and maturation of fetal organs through increasing adrenal functions, glycogen deposition and active gluconeogenesis, fatty acid

oxidation, lung and liver maturity plus other more.

Conclusion

In communities where the incidence of consanguinity is high, phenotypically female babies presenting with IUGR in presence of skin hyperpigmentation should alert the clinician to the possible diagnosis of lipoid form of CAH.

Consent

Written consent was obtained from parents for publication.

Conflict of Interest

The authors declare that they had no conflict of interest in reporting and publication of this paper.

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