Phenotypic Variability in Congenital Lipoid Adrenal Hyperplasia

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Received: July 26. 2013;
Initial review: October 04, 2013;
Accepted: February 05, 2014.

Background: Congenital lipoid adrenal hyperplasia presents with adrenal insufficiency and sex reversal in 46XY genetic males. **Case characteristics**: Two patients (46 XY karyotype), one having ambiguous genitalia and other having female external genitalia, presented with adrenal crisis at 6 months and 4 weeks of age, respectively. **Observation**: *Steroidogenic Acute Regulatory Protein* gene sequencing revealed homozygous mutations in both patients. **Outcome**: Treatment with hydrocortisone and fludrocortisone resulted in marked improvement . **Message**: Congenital lipoid adrenal hyperplasia should be considered in infants having female or ambiguous genitalia, and presenting with adrenal insufficiency.

Keywords: Adrenal crisis, Ambiguous genitalia, Sex reversal.

Congenital lipoid adrenal hyperplasia (CLAH) due to *steroidogenic acute regulatory protein (STAR)* gene mutations is the most severe form of congenital adrenal hyperplasia, in which all steroidogenesis is impaired in adrenals and gonads. This results in all individuals – regardless of karyotype – having female external genitalia, hyponatremia, hyperkalemia, acidosis and shock [1]. Though children with 46 XY karyotype have complete sex reversal, few cases with mild genital virilization have been reported. We report two patients having CLAH with such phenotypic variability.

CASE REPORTS

Case 1: A two-month old girl born out of consanguineous union was referred for frequent vomiting, failure to thrive and increasing dark pigmentation of skin. She had previous admissions at 4 and 7 weeks of life for severe dehydration, and in one such admission she was found to have hyponatremia (serum sodium- 113 mEq/L), hyperkalemia (serum potassium- 6.5 mEq/L) and metabolic acidosis (pH-7.2, bicarbonate18 mEq/L). She weighed 4 kg (birth weight 3 kg) with length of 61 cm, and had normal external female genitalia without palpable gonads. A provisional diagnosis of primary adrenal insufficiency was made. Blood investigations were: serum sodium 113 mEq/L , potassium 6.4 mEq/L, glucose 80 mg/dL, cortisol <1 µg/dL, ACTH 3320 pg/mL and 17-hydroxy-progesterone (17OHP)- 0.58 ng/mL (N:0.07-1.7 ng/ml). Abdominal imaging revealed nodular hyperplasia of adrenals and inguinal testis (retracting intra-abdominally) with absence of mullerian structures. Further investigtions showed: Serum testosterone <0.01 ng/mL (no rise after HCG stimulation), dehydroepiandrosterone (DHEA) 0.28 ng/mL, androstenidione <0.3 ng/mL and 46XY karyotype. Complete sequencing of the *STAR* gene revealed homozygous mutation c.441G>A (p.W147X).

Case 2: A six-month-old child born out of consanguineous union and reared as girl was brought with adrenal crisis. She also had failure to thrive and dark pigmentation of skin. She had a weight of 4 kg (birth weight 2.75 kg) and length of 64 cm. Genital examination revealed phallus of 2 cm, partial fusion of labioscrotal folds with palpable gonads, and single opening at junction of phallus and labioscrotal folds. Investigations revealed: serum Na 119 mEq/L, serum K 7.8 mEq/L, blood pH 7.23, serum bicarbonate 8 mEq/L, glucose 39 mg/dL, cortisol 7.83 µg/dL (30 and 60 min after ACTH stimulation 9 and 8.4 µg/dL, respectively), ACTH 12490 pg/mL, testosterone <0.08 ng/mL (no rise after HCG stimulation), DHEA 17.3 ng/mL, androstenidione 0.34 ng/mL, 17-OHP 0.43ng/mL, and 46XY karyotype. Abdominal imaging revealed inguinal canal testes, normal adrenals and absence of mullerian structures. Sequencing of the *STAR* gene revealed homozygous mutation c.544C>T (p.R182C).

Both patients were treated with hydrocortisone, fludrocortisone and oral salt. The parents of second patient decided to rear their child as boy.

DISCUSSION

STAR mutations are found commonly in Japanese, Korean and Palestinian populations but are rarely reported elsewhere [2]. The human *STAR* gene is localized on chromosome 8p11.2 [3]. *STAR* mediates the rapid action of ACTH on the adrenal and of luteinizing hormone (LH) on the gonad by facilitating rapid movement of cholesterol from the outer to the inner mitochondrial membrane where it is converted to pregnenolone. According to the the two-hit model explaining the pathophysiology of CLAH, this transfer into the mitochondria does not happen (first hit) resulting in increased ACTH secretion and subsequently increased cholesterol production that accumulates as lipid

droplets in adrenal cells. This damages the architecture by mechanical displacement and auto-oxidation (second hit) [3].

Patients with CLAH typically present with a salt losing crisis in the first 2 months of life (most of them in the first month) and those with 46XY karyotype have female genitalia because testosterone synthesis is impaired during fetal development [4]. One of our patient had classic presentation of CLAH while the other had atypical presentation marked by mild virilization of genitals and adrenal crisis at 6 months.The differential diagnoses considered in the first patient (with sex reversal) were, congenital adrenal hypoplasia due to SF-1 mutation, mutation of side chain cleavage enzyme (CYP11A1) gene and Smith Lemli Opitz syndrome. However, adrenal hyperplasia on imaging made us suspect *STAR* mutation. The differential diagnoses considered in second patient were congenital adrenal hypoplasia due to *DAX*-1 mutation, 3ß- hydroxysteroid dehydrogenase (3ßHSD) deficiency and p-450 oxidoreductase (POR) deficiency. Molecular genetic analysis of *DAX*-1 and *3ßHSD* genes, in our patients, revealed no abnormality. Normal 17-OHP level, and absence of craniofacial anomalies or maternal virilization during pregnancy, suggested a diagnosis of POR deficiency to be unlikely. CLAH may rarely present with ambiguous genitalia or even normal male genitalia with delayed clinical manifestations [5-7]. This prompted us to do molecular genetic analysis for *STAR* gene mutation in the second patient. At presentation this patient had detectable cortisol, DHEA and androstenidione levels indicating some production of adrenal steroids indicating partial adrenal steroid defect. This could happen before enough accumulation of lipid to destroy residual steroidogenesis of adrenal gland (second hit) [6]. A significantly elevated ACTH and poor response to ACTH stimulation clearly indicated poor adrenal hormone response. Bhangoo, *et al*. [2] have reported a case with homozygous missense mutation of c.544CÿT (p.R182C) in exon 5 in genotypic male patients with delayed presentation – quite similar to our second patient with the same mutation.

This report demonstrates that CLAH is a disease with variable clinical manifestation and phenotypic spectrum. CLAH should be considered in infants with female or ambiguous genitalia and adrenal insufficiency. A molecular genetic analysis helps firmly secure the diagnosis, and helps to give genetic counseling for future pregnancies.

Acknowledgement: We are grateful to Dr YK Amdekar, Medical Director, BJ Wadia Hospital for Children, for allowing us to publish this case report.
Contributors: JR: diagnosed and managed the patients and drafted the article. DD and TP: performed the molecular genetic analysis. SS was involved in management of the patients.
Funding: None. *Competing interests*: None stated.

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