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A Rare Case of Lipoid Congenital Adrenal Hyperplasia

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1. INTRODUCTION

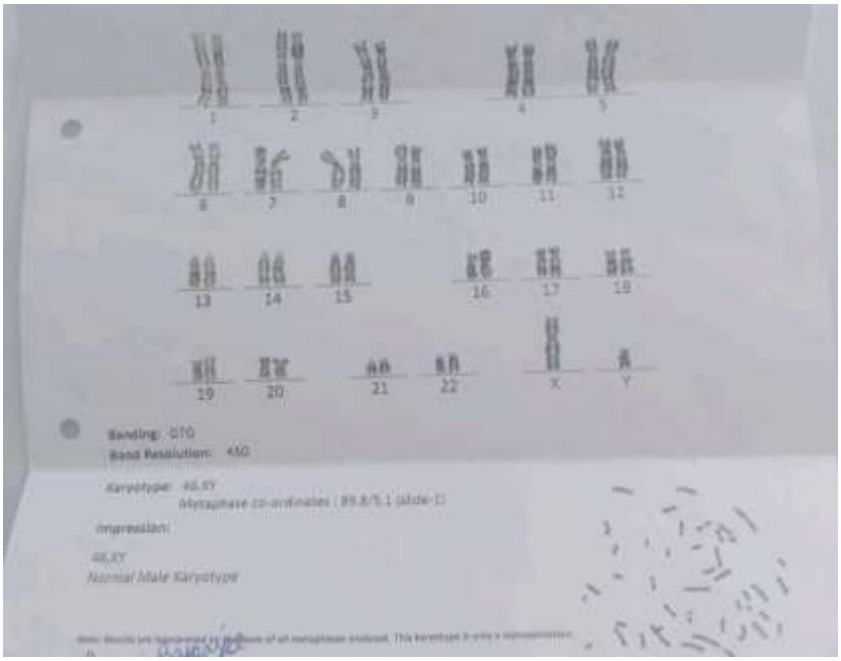
Congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders characterized by defects in enzymes or proteins involved in adrenal steroidogenesis. Among these, lipoid congenital adrenal hyperplasia (LCAH) represents the most severe and rare form, caused by mutations in the *Steroidogenic Acute Regulatory* (*STAR*) gene. LCAH results in impaired cholesterol transport into mitochondria, leading to a near-complete deficiency of all adrenal and gonadal steroids [2]. Infants with LCAH often present within the first few months of life with non-specific symptoms such as poor feeding, vomiting, failure to thrive, and dehydration, progressing rapidly to life-threatening adrenal crises if unrecognized [1]. Genetic males (46,XY) typically exhibit varying degrees of under-virilization due to impaired testosterone synthesis, while genetic females (46,XX) usually have normal female external genitalia. Early diagnosis is critical to initiate appropriate glucocorticoid and mineralocorticoid replacement therapy and prevent morbidity and mortality. However, due to its rarity and overlapping features with more common forms of CAH, LCAH can be easily misdiagnosed, leading to delays in treatment [4]. We report a case of a four-month-old male infant who presented with hyponatremic dehydration, failure to thrive, and features of adrenal insufficiency. Genetic analysis revealed a homozygous pathogenic variant in the *STAR* gene, confirming the diagnosis of lipoid congenital adrenal hyperplasia.

CASE REPORT

4 months old male child was brought to the tertiary care centre by parents with complains of poor feeding since 15 days, decreased urine output since 7 days, vomiting since 3 days. Mother noticed child was not brestfeeding like before since last 15 days. Mother was also complaining that child had passed urine only 2-3 times in a day since last 7 days. Child had 3-4 episodes of vomiting in a day since last 3 days. Vomiting was non projectile. Vomitus was non billious, non blood stained containing milk. There was history of 7% weight loss over last 15 days. Child had simillar complaints around one month back for which he was admitted in hospital for 5 days and treated with IV fluids. Baby was first born child out of non consanguineous marriage, delivered via LSCS in view of Meconium-stained liquor with birth weight of 2.75 kg at term gestation. Exclusive breast feeding was initiated in operation theater soon after birth. All antenatal scans along with anomaly scan and fetal 2D echo was normal. Baby was vaccinated up to 14 weeks according national immunization schedule. On admission child was irritable and poorly accepting feeds with tachycardia and tachypnea with depressed fontanelle; sunken eyes; skin turgor goes back slowly [skin pinch > 2sec]; capillary refile time >3sec and dry oral mucosa. Child looked severely dehydrated with cold extremities and low volume peripheral pulses and hypotension. Genital examination showed small phallus of 1.8 cm [normal stretched penile length 2.22 to 4.46 cm with mean length of 3.34 cm] and left sided undescended testis without penoscrotal hypospadias. Blood investigation showed hyponatremia [Serum sodium level of 117 mmol/L] with hyperkalemia [Serum potassium level of 5.44 mmol/L] and hypochloremia [Serum chloride level of 95 mmol/L] with raised

serum urea [108 mg/dl] and elevated serum creatinine [0.63mg/dl] level. Child was first treated for hyponatraemic dehydration affecting renal function. After initial stabilisation child was further evaluated for hyonatremic dehydration which showed Low level of serum 17 hydroxy progesterone [<0.1 ng/L] , serum aldosterone [29.56 pg/L] , and serum cortisol level [3.40 microgram/L]. Above investigations are suggestive of congenital adrenal hyperplasia which was affecting glucocorticoids; and mineralocorticoids synthesis. Further evaluation showed raised level of serum ACTH [>1250 pg/mL] and serum renin level [>1000 microIU/mL]; with normal levels of serum FSH [6.02 mIU/mL] and serum LH [26.14 IU/mL]. Above investigations are suggestive of normal functioning of hypothalamus pituitary axis. Child was further evaluated on Karyotyping and whole exome sequencing to confirm STAR gene mutation.

Chromosomal analysis showed normal male genotype.



Whole exome sequencing showed homozygous for a likely pathogenic variant in the STAR gene associated with LIPOID CONGENITAL ADRENAL HYPERPLASIA.

FINDINGS RELATED TO PHENOTYPE

Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classifcation
STAR NM_000349.3	c.767_769delTCA p.Ile256del	Exon 7	Homozygous	-	LIPOID CONGENITAL ADRENAL HYPERPLASIA; LCAH:201710	Autosomal Recessive	Likely Pathogenic

* Genomic Position based on Assembly GRCh37, **Number of applied in silico programs predicting the effect of the variant on the protein outcome (CADD: Combined Annotation Dependent Depletion (v1.6), SIFT, PolyPhen-2, MT: Mutation Taster), N/A: Not Applicable, ***Minor Allele Frequency as described in GnomAD (Controls), ****based on ACMG Guidelines. het=heterozygous, hom=homozygous, hemi=hemizygous.

2. DISCUSSION:

Lipoid congenital adrenal hyperplasia (LCAH) is a rare and potentially life-threatening disorder of steroidogenesis resulting from mutations in the *STAR* (Steroidogenic Acute Regulatory) gene. The presented case highlights the classical features of LCAH in an infant: failure to thrive, vomiting, poor feeding, dehydration, electrolyte imbalance (hyponatremia and hyperkalemia), ambiguous genitalia (small phallus, undescended testis), and shock secondary to adrenal insufficiency. The clinical presentation of severe dehydration, hypotension, and electrolyte disturbances is characteristic of salt-wasting crises often seen in primary adrenal insufficiency. In this case, biochemical evaluation showed marked hyponatremia (117

mmol/L), hyperkalemia (5.44 mmol/L), elevated serum urea (108 mg/dL), and creatinine (0.63 mg/dL), all indicative of impaired mineralocorticoid function and acute kidney injury secondary to volume depletion. A distinguishing feature of LCAH compared to classic 21-hydroxylase deficiency — the most common cause of congenital adrenal hyperplasia (CAH) — is the presence of low serum 17-hydroxyprogesterone, cortisol, and aldosterone levels, along with markedly elevated ACTH and plasma renin levels [1]. This was confirmed in the present case, where serum 17-hydroxyprogesterone (<0.1 ng/L), aldosterone (29.56 pg/L), and cortisol (3.40 µg/dL) were low, while ACTH (>1250 pg/mL) and renin (>1000 µIU/mL) were significantly elevated. In LCAH, mutations in the *STAR* gene impair the transport of cholesterol into mitochondria, a critical initial step in steroidogenesis [2]. The resultant lack of cortisol, aldosterone, and sex steroids explains both the adrenal insufficiency and the disordered sexual development observed in 46,XY individuals. Interestingly, in this patient, despite normal male karyotype (46,XY) confirmed by chromosomal analysis, genital examination revealed a small phallus and undescended testis without hypospadias, consistent with partial under-masculinization. The definitive diagnosis was established through whole exome sequencing, which revealed a homozygous likely pathogenic variant in the *STAR* gene. Molecular diagnosis is crucial for confirming LCAH, guiding management, and offering genetic counseling for the family [3]. Management includes acute stabilization with intravenous fluids and correction of electrolyte abnormalities, followed by lifelong glucocorticoid and mineralocorticoid replacement therapy [4]. Early recognition and treatment are vital to prevent adrenal crises and optimize growth and development outcomes. This case underscores the importance of considering LCAH in any neonate or infant presenting with salt-wasting crises, ambiguous genitalia (even if mild), and biochemical evidence of adrenal insufficiency with low 17-hydroxyprogesterone levels. Prompt genetic testing and initiation of steroid replacement are critical steps in improving prognosis.

3. CONCLUSION:

Lipoid congenital adrenal hyperplasia (LCAH) is a rare but severe form of adrenal insufficiency that can present early in infancy with life-threatening salt-wasting crises, failure to thrive, and varying degrees of genital ambiguity in genetic males. This case emphasizes the importance of considering LCAH in the differential diagnosis of any infant with hyponatremic dehydration, particularly when standard markers for classic CAH (such as 17-hydroxyprogesterone) are not elevated. Early biochemical assessment, genetic confirmation, and timely initiation of steroid replacement therapy are critical to prevent adrenal crises, improve growth outcomes, and enable appropriate long-term care, including genetic counseling for affected families.

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