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Congenital lipoid adrenal hyperplasia in a Saudi infant

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Summary

Congenital lipoid adrenal hyperplasia (CLAH) is characterized by a defect in the STAR protein-encoding gene that attenuates all steroidogenesis pathways. Herein, we present the first reported case in Saudi Arabia of a 46 XY, phenotypically female infant with an unfamiliar, darkened complexion compared to the family's skin color. Based on the clinical and biochemical findings, CLAH was diagnosed and glucocorticoid replacement therapy was initiated. As a result, we suggest that pediatricians should always investigate the possibility of adrenal insufficiency when encountering unusual dark skin.

Learning points:

- Pediatricians should be prompted to rule out adrenal insufficiency in unexpectedly dark skin neonates.
- In such patients, pediatricians should not wait until the neonate develops an adrenal crisis.
- A low level of 17-hydroxyprogesterone does not always rule out the possibility of inherited adrenal gland disorders, and additional tests should be performed for early detection.

Background

Although congenital lipoid adrenal hyperplasia (CLAH) is uncommon, it is the most severe form of inherited adrenal disorder passed down through families in an autosomal recessive manner and was first described by Prader *et al*. in 1955 (1). In this disease, the principal defect lies in the gene encoding the STAR protein locus in the 8p11.2 region (2). STAR plays an indispensable role in facilitating the transfer of cholesterol from the outer to the inner mitochondrial membrane (3). Once within the mitochondria, cholesterol is converted to pregnenolone by the cytochrome P450 side-chain cleavage (CYP11A1) enzyme, initiating steroid biosynthesis. Consequently, the disease is characterized by the impairment of steroid biosynthesis in the adrenal glands and gonads. Affected neonates present with hyperkalemia, hyponatremia, metabolic acidosis, shock, and female external genitalia regardless of karyotype – as 46, XY genetic males fail to produce testosterone (4). Here, we present an extremely rare case of CLAH in a Saudi infant.

Case presentation

A 4-month-old Saudi infant with dark skin was born into a fair-skinned household, at 38 weeks of gestational age, weighing 2.7 kg at birth. Both parents had double consanguinity, with no history of previous abortions, neonatal deaths, or medical illnesses (Fig. 1). Initially, the neonate was active and feeding well with no other symptoms. General examination revealed no dysmorphic features with unexplained generalized skin hyperpigmentation, including completely normal external female genitalia with no palpable gonads (Fig. 2). However, at 5 days old, the neonate started to manifest poor feeding, activity, and weight gain associated with severe

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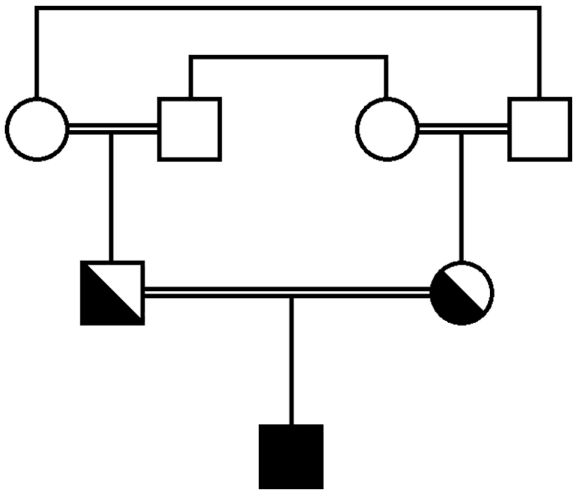

Figure 1
The pedigree of double consanguine grandparents and parents with the affected neonate.

Figure 2
Neonate at age 7 days presenting with generalized hyperpigmentation.

hypoglycemia. Adrenal insufficiency was suspected at the time of assessment, and the results of the biochemical tests are listed in Table 1. Chromosomal analysis revealed 46 XY, while ultrasound of the abdomen revealed bilateral undescended testicles with no internal female genital structures and bilateral enlarged adrenal glands. Based on these clinical, biochemical, chromosomal, hormonal, and radiological findings, CLAH was suspected and confirmed by the results of whole-exome sequencing which identified a homozygous pathogenic variant in the *STAR* gene consistent with the genetic diagnosis of autosomal recessive CLAH.

As per management, glucocorticoid replacement therapy (dose of 12 mg/m^2/day divided into 3 doses) was initiated, and the neonate was assigned the sex of female, regardless of the 46, XY karyotype, because of the normal female external genitalia despite the absence of internal female structures. Follow-up at the clinic 4 weeks later confirmed the reversal of the darkened skin color to the family's fair skin color (Fig. 3).

Discussion

In this case report, we described the medical history, examination, and management of a Saudi infant with CLAH caused by a STAR gene mutation who presented with hyperpigmentation.

Table 1 Laboratory findings revealed a negative septic workup with significantly high adrenocorticotropic hormone (ACTH) and renin. Low levels of cortisol, aldosterone, 17-hydroxyprogesterone, and adrenal androgens.

Parameters	Values	Normal range
Hemoglobin, g/dL	16.3	10.4–16
White blood cells, ×1000/μL	9.3	6–18
Platelets, ×1000/μL	243	150–450
Blood culture	Negative	Negative
Urine culture	Negative	Negative
Cerebral spinal fluid culture	Negative	Negative
Bicarbonate, mmol/L	13	20–31
Sodium, mmol/L	126	135–145
Potassium, mmol/L	6.6	3.5–5.1
Urea, mmol/L	10	3.2–8.2
Creatinine, μmol/L	90	62–115
ACTH, pg/mL	1222	6–76
Cortisol	50 nmol/L	2.2–35.3 ng/dL
Renin, μIU/mL	>500	4.5–46.2
Aldosterone, ng/dL	3.3	2.2–35.6
Testosterone	0.3 nmol/L	0.2–17.2 ng/mL
DHEAS, μg/dL	11	11–120
17-hydroxyprogesterone	0.96 ng/mL	0–17.3 nmol/L

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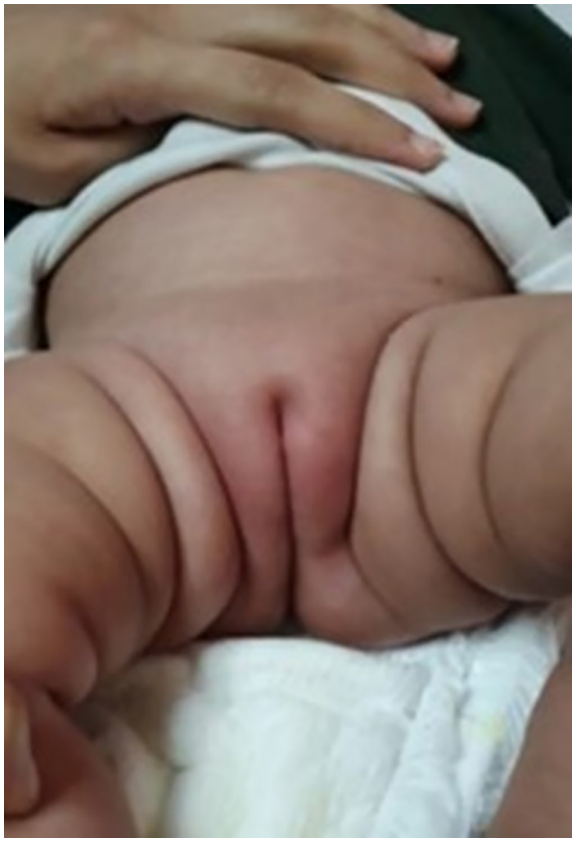

Figure 3
Infant at age 4 months with normal female external genitalia and fair skin color post-treatment.

CLAH is a congenital adrenal steroidogenic disorder that involves a deficiency of all – or nearly all – adrenal and gonadal steroid hormones. When adrenal and gonadal steroid hormones are absent, CLAH is both the most fatal and one of the rarest forms of congenital adrenal steroidogenic defects. CLAH is thought to occur because of a gene mutation in chromosome 8, which encodes the mitochondrial phosphoprotein STAR, attenuating all pathways of steroidogenesis.

Neonates with complete CLAH due to STAR mutations often have severe adrenal insufficiency shortly after delivery. However, symptoms like vomiting, diarrhea, volume depletion, hyponatremia, and hyperkalemia may only occur later in infancy. Male neonates classically present with female external genitalia because of the lack of testicular androgen production. Contrastingly, female neonates are fully developed at birth, and some females experience spontaneous partial pubertal development (5). Males with non-classic CLAH may still have adrenal insufficiency, regardless of normal external genitalia.

The first case of CLAH was reported in Thailand in 1995 (1). Other cases have been predominantly reported among Korean, Japanese, and Palestinian populations, despite the rarity of the disease and low global occurrence (6). However, this is the first reported case of its kind in Saudi Arabia.

In this case, the neonate's skin color served as both a hint and a leading indicator for further investigations since hyperpigmentation can indicate CLAH. Other differential diagnoses of generalized hyperpigmentation in newborns and infants include Cushing's syndrome, hyperthyroidism, chronic hepatic, and renal illness, and oral or topical drugs (7). Hyperpigmentation is caused by a high level of serum adrenocorticotropic hormone due to adrenal insufficiency, which can result from several disorders including congenital adrenal hyperplasia, CLAH, congenital adrenal hypoplasia, hypoxia, sepsis, and adrenal hemorrhage (8). Among these causes, CLAH was diagnosed in this newborn with the help of genetic analysis. Thus, every child born with a dark complexion that differs from the rest of their family should be suspected of having congenital adrenal hyperplasia. Laboratory findings in neonates with CLAH show low serum cortisol and aldosterone levels, extremely high serum adrenocorticotropic hormone levels and plasma renin activity. Additionally, as in this patient's case, they can also show low serum 17-hydroxyprogesterone (17-OHP) and adrenal androgen levels. It should be noted that the 17-OHP level is a screening measure utilized in newborn screening programs (9). It is generally high at birth, but it diminishes within the first few days following delivery in healthy neonates. However, 17-OHP gradually rises in children with CLAH. Hence, its low accuracy in the first few days. In preterm infants, ill newborns, and small for gestational age and stressed neonates, 17-OHP levels may be falsely elevated (10). The causes of low 17-OHP include lipoid adrenal hyperplasia, 17-alpha-hydroxylase enzyme deficiency, and 17, 20 lyase deficiency. As a result, the screening test is routinely performed after 48 h, and after a positive result is obtained, it should always be verified by a second confirmatory test (10).

Finally, in an unexpectedly dark-skinned neonate, adrenal insufficiency should be ruled out rather than waiting until the neonate develops an adrenal crisis. Pediatricians should be aware that a low level of 17-OHP does not always rule out the possibility of inherited adrenal gland disorders and that additional tests should be performed for early detection.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of patient's clinical details and/or clinical images was obtained from the parents.

Author contribution statement
Conceptualization, A A; investigation, S S, R W; resources, S S, R W and A A; Writing – original draft preparation, S S, R W; writing – review and editing, S S, R W and A A; supervision, A A; visualization S S, R W and A A; project administration, A A; funding acquisition, None. All authors have read and agreed to the published version of the manuscript.

References

1 Jaruratanasirikul S. P450scc deficiency (congenital lipoid adrenal hyperplasia): first reported case in Thailand and literature review. *Journal of the Medical Association of Thailand* 1996 **79** 531–535.
2 Miller WL & Gucev ZS. Chapter 3I – Disorders in the initial steps in steroidogenesis. In *Genetic Steroid Disorders*, pp. 145–164. Eds MI New, O Lekarev, A Parsa, TT Yuen, BW O'Malley & GD Hammer. San Diego: Academic Press, 2014. (https://doi.org/10.1016/B978-0-12-416006-4.00011-9)
3 Baker BY, Lin L, Kim CJ, Raza J, Smith CP, Miller WL & Achermann JC. Nonclassic congenital lipoid adrenal hyperplasia: a new disorder of the steroidogenic acute regulatory protein with very late presentation and normal male genitalia. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 4781–4785. (https://doi.org/10.1210/jc.2006-1565)
4 Joshi R, Das D, Tamhankar P & Shaikh S. Phenotypic variability in congenital lipoid adrenal hyperplasia. *Indian Pediatrics* 2014 **51** 399–400.
5 Fujieda K, Tajima T, Nakae J, Sageshima S, Tachibana K, Suwa S, Sugawara T & Strauss 3rd JF. Spontaneous puberty in 46,XX subjects with congenital lipoid adrenal hyperplasia. Ovarian steroidogenesis is spared to some extent despite inactivating mutations in the steroidogenic acute regulatory protein (STAR) gene. *Journal of Clinical Investigation* 1997 **99** 1265–1271. (https://doi.org/10.1172/JCI119284)
6 Fu R, Lu L, Jiang J, Nie M, Wang X & Lu Z. A case report of pedigree of a homozygous mutation of the steroidogenic acute regulatory protein causing lipoid congenital adrenal hyperplasia. *Medicine* 2017 **96** e6994. (https://doi.org/10.1097/MD.0000000000006994)
7 Dabas G, Vinay K & Mahajan R. Diffuse hyperpigmentation in infants during monsoon season. *JAMA Dermatology* 2020 **156** 99–101. (https://doi.org/10.1001/jamadermatol.2019.3070)
8 Buonocore F & Achermann JC. Primary adrenal insufficiency: new genetic causes and their long-term consequences. *Clinical Endocrinology* 2020 **92** 11–20. (https://doi.org/10.1111/cen.14109)
9 Anandi VS & Shaila B. Evaluation of factors associated with elevated newborn 17-hydroxyprogesterone levels. *Journal of Pediatric Endocrinology and Metabolism* 2017 **30** 677–681. (https://doi.org/10.1515/jpem-2016-0459)
10 Kim CJ. Congenital lipoid adrenal hyperplasia. *Annals of Pediatric Endocrinology and Metabolism* 2014 **19** 179–183. (https://doi.org/10.6065/apem.2014.19.4.179)

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