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STAR gene mutation in a patient with congenital lipoid adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) is a group of diseases characterized by genetic defects in the proteins and enzymes involved in cortisol biosynthesis. Reduced cortisol production weakens the feedback inhibition of cortisol on the pituitary gland, resulting in increased adrenocorticotropic hormone (ACTH) production. Elevated ACTH causes adrenal cortical hyperplasia and promotes to increased production of cortisol precursors [1]. Congenital lipoid adrenal hyperplasia (CLAH) is the rarest and most severe form of CAH. Most cases are caused by mutations in the STAR gene and a few are caused by mutations in the CYP1IAI gene [2]. The incidence of this disease is low, as there are only 200 reported cases of STAR gene mutations worldwide [3].

A 34-year-old female patient was admitted with fever and poor appetite for 4 days. She had a fever of 39.0°C, low blood pressure (64/46 mm Hg), and hyponatremia (131.2 mmol/L), accompanied by poor appetite, fatigue, and decreased food intake. The treatment included fluid resuscitation, sodium replacement, and anti-infective therapy, but hypotension and hyponatremia persisted. She had a poor mental state, appetite, and sleep quality, and exhibited childhood growth delays and cognitive impairment. She reported having one menstrual period at the age of 13 years, but the specific amount and duration are unknown. She has not been married or had children.

The patient's body temperature was 37.6°C, respiratory rate was 28 breaths per minute, pulse was 120 beats per minute, and blood pressure was 83/56 mm Hg. The patient was alert, but had a poor mental status, with a thin stature, a pallor suggesting anemia, and dark, dull, and rough skin throughout her body. Her voice was childish. Her eyebrows were pale and sparse, and her lips were dark-brownish in color. Pigment deposition was evident on the tongue, gums, and nails (Fig. 1). There was no axillary or pubic hair, and the Tanner stage was B3P2.

After admission, further examinations were conducted. The 8-AM ACTH > 440.40 pmol/L (N: 1.60–13.90) and 8-AM cortisol of 2.79 nmol/L (N: 68.20–327.00). Sex hormone levels were abnormal, with 17-hydroxyprogesterone < 0.50 nmol/L (N: 0.60–4.00) and androstenedione < 0.44 nmol/L (N: 1.22–8.73). The 21-deoxycortisol and 11-deoxycortisol levels values < 0.13 nmol/L (N: <0.14) and < 0.10 nmol/L (N: < 1.47), respectively. The anti-Müllerian hormone level was 1.51 ng/mL (N: 0.67–10.92). Thyroid function tests revealed elevated levels of thyroid-stimulating hormone at 11.080 mIU/L (N: 0.270–4.200) and low free thyroxine (FT4) at 10.38 pmol/L (N: 12.00–22.00). Thyroid peroxidase antibody (TPOAb) was significantly increased at 455.20 IU/mL (N: ≤34.00) and thyroglobulin antibody (TGAb) was also elevated at 273.90 IU/mL (reference range: ≤ 115.00). Gynecological ultrasound indicated a smaller uterus ($3.2 \times 2.4 \times 1.2$ cm^3), intact capsule, uniform myometrium, unclear endometrial line, and unclear visualization of both ovaries. Peripheral blood chromosomal karyotyping analysis revealed a normal female karyotype of 46, XX. Genetic testing revealed the patient carried two compound heterozygous pathogenic variants in the STAR gene, specifically NM_000349.3:c.815G>A (p. Arg272His) and NM_000349.3:c.229C>T (p. Gln77*). The father carried NM_000349.3:c.815G>A (p. Arg272His) and the mother carried NM_000349.3:c.229C>T

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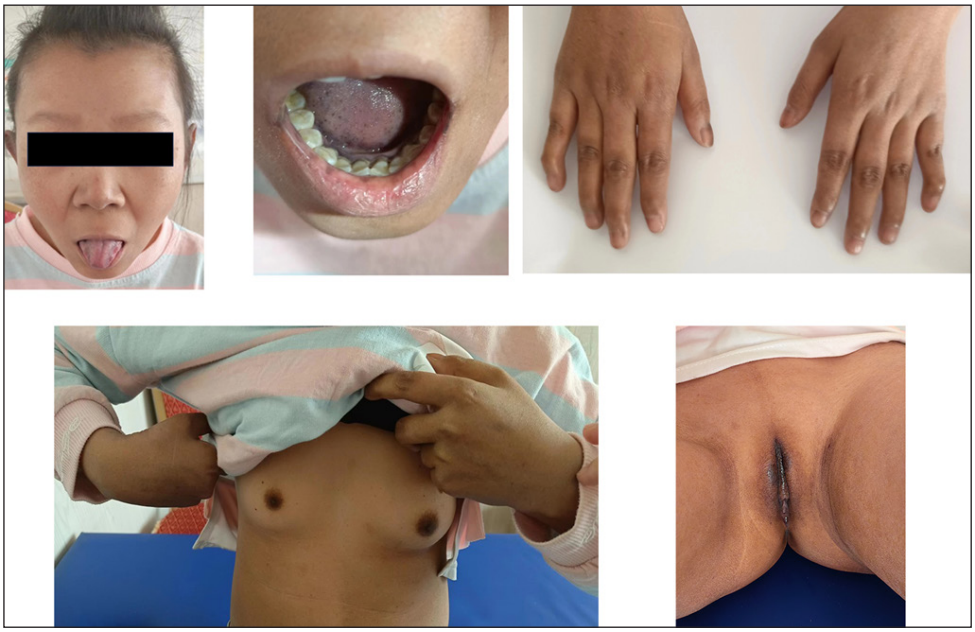

Figure 1. *Patient's generalised skin and mucous membrane pigmentation*

(p. Gln77*). Based on this data, the diagnosis was CLAH [MIM: 201710].

After admission, the patient presented with fever, poor appetite, low blood pressure, and low blood sodium, suggesting an adrenal crisis. Initial treatment involved intravenous hydrocortisone for 3 days (200 mg/day, 100 mg/day, and 50 mg/day), followed by oral prednisone (20 mg in the morning; 10 mg at 16:00, tapering to 5 mg in the morning; and 2.5 mg at 16:00). The patient experienced significant improvement in appetite and mental status. Blood pressure was maintained at 90–115/52–88 mmHg, and blood sodium fluctuated between 138.6 and 140 mmol/L. Upon stabilization, the patient was discharged.

In this case, we report a female CLAH patient with STAR gene mutation and typical skin pigmentation. She was diagnosed with adrenal crisis, but previously had no specific symptoms and did not seek medical treatment. CLAH typical manifests as adrenal cortical insufficiency, salt loss, and abnormal sexual development. Adult CLAH patients with adrenal insufficiency symptoms, such as anorexia, fatigue, hypotension, low sodium, and low blood sugar, should be monitored for adrenal crisis and treated promptly. The heterozygous pathogenic variants c.815G>A (p. Arg272His) and c.229C>T (p. Gln77*) are pathogenic mutations. Genetic sequencing and analysis in adult-onset patients provide valuable information on the characteristics, diagnosis and treatment of CLAH.

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Ethics statement
The authors certify that they have obtained all appropriate patient consent forms. In this case, the patient and her family gave her/their consent for images and other clinical information to be reported in the journal.

Author contributions
Y.Z.: writing — original draft, data curation, conceptualization; C.S.: writing — original draft, data curation; L.Z.: data curation, writing — review and editing; L.S.: writing — review and editing; Q.Z.: writing — review and editing, conceptualisation, and supervision; Y.Z. and C.S. contributed equally to this work as co-first authors; Q.Z. is the corresponding author of this work.

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Conflict of interest
Authors declare no conflict of interests.

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