

High-dose fludrocortisone therapy was transiently required in a female neonate with 21-hydroxylase deficiency

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Highlights

- A neonate with 21OHD transiently required high-dose FC of > 0.4 mg/d.

Abstract. For salt-wasting 21-hydroxylase deficiency (21OHD), fludrocortisone (FC) is usually supplemented at 0.05–0.2 mg/d dose. To date, no report has described 21OHD neonates requiring > 0.4 mg/d of FC. Our female 21OHD patient was lethargic and experienced weight loss with hyponatremia (133 mEq/L), hyperkalemia (6.5 mEq/L), and elevated active renin concentration (ARC, 1942.2 pg/mL) at 6 days of life. Hydrocortisone and FC replacement were initiated. FC dose was gradually increased to 0.4 mg/d at 21 days of life, but her hyperkalemia (6.4 mEq/L) and high ARC (372.3 pg/mL) persisted. We increased FC to 0.6 mg/d and used a low-potassium and high-sodium formula. Hyperkalemia subsequently improved. At 33 days of life, the ARC decreased to 0.6 pg/mL and FC dosage was gradually decreased. At 3 months of age, the low-potassium and high-sodium formula was discontinued, but the serum potassium level was normal and ARC remained low at 0.1 mg/d of FC. We speculated that severe mineralocorticoid resistance was the reason why her hyperkalemia persisted even with 0.4 mg/d of FC; however, the pathophysiology of transiently severe resistance to FC in this patient is unknown. In conclusion, 21OHD neonates may show severe salt-wasting that transiently require > 0.4 mg/d of FC.

Key words: fludrocortisone, high-dose, 21-hydroxylase deficiency, salt wasting

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Introduction

21-hydroxylase deficiency (21OHD) is the most common cause of congenital adrenal hyperplasia. 21OHD is classified into severe salt-wasting, less severe simple-virilizing, and the least severe non-classic forms. Patients with salt-wasting 21OHD experience weight loss, poor feeding, dehydration, hyponatremia, and hyperkalemia owing to cortisol and aldosterone deficiencies usually during the second week of life (1, 2). Treatment for salt-wasting 21OHD includes hydrocortisone (HC) and fludrocortisone (FC), potent glucocorticoids, and mineralocorticoids. FC is usually supplemented at 0.05–0.2 mg/d dose, and some affected neonates may require up to 0.4 mg/d FC (3). To date, no report has described affected neonates requiring > 0.4 mg/d of FC. Here, we report a neonate with 21OHD whose hyperkalemia was not normalized with 0.4 mg/d of FC administration.

Case Report

The clinical course of the patient is summarized in **Fig. 1**. The patient was the first child of healthy non-consanguineous Japanese parents. The pregnancy was uncomplicated, and the mother delivered vaginally at 40 wk of gestation without asphyxia. The birth weight of the neonate was 3210 g (+ 0.64 standard deviation) and the length was 49.0 cm (–0.24 standard deviation). Clitoromegaly and labial fusion were observed on the first day after birth. She was referred to our hospital after six days of life. She was lethargic, and her weight had decreased by 96 g since the previous day. Blood examinations showed hyponatremia (133 mEq/L), hyperkalemia (6.5 mEq/L), elevated active renin concentration (ARC; 1942.2 pg/mL, reference for adults, 3.2–36.3), normal creatinine levels (0.42 mg/dL; reference for neonates of 6 days of life, 0.32–0.52), and elevated adrenocorticotropic hormone (1060 pg/mL; reference for adults, 7.2–63.3). We tentatively diagnosed the patient with adrenal crisis and initiated treatment with fluid replacement and continuous intravenous HC injection in saline at 100 mg·m⁻²·d⁻¹. Ultrasonography revealed swelling of the adrenal glands without lobulation. The filter paper blood 17 α -hydroxyprogesterone concentration was 122.2 ng/mL. The urine steroid profile showed elevated pregnanetriolone (4.604 mg/gCr; age-specific cutoffs of 0–10 days of life, 0.06) and elevated ratios of 11 β -hydroxyandrosterone/tetrahydroaldosterone and 11 β -hydroxyandrosterone/pregnanediol (30.65 and 1.83, respectively; the cutoffs to distinguish between 21OHD and P450 oxidoreductase deficiency, 0.80 and 1.0, respectively) (4). Therefore, the patient was diagnosed with 21OHD. At 7 days of life, her poor sucking ability improved. At 9 days of life, the serum concentrations of sodium (137 mEq/L) and potassium (5.6 mEq/L) were normal and creatinine levels decreased (0.26 mg/dL). On the same day, intravenous administration of HC was discontinued and oral HC administration was

changed to 60 mg·m⁻²·d⁻¹. At 11 days of life, she became lethargic and again showed poor sucking. Her weight had decreased by 400 g on the previous day. Blood tests revealed hyponatremia (130 mEq/L), hyperkalemia (7.7 mEq/L), and elevated ARC (1946.8 pg/mL). She had no signs of infection such as fever, apnea, vomiting, elevated C-reactive protein level, or high white blood cell count. The patient was diagnosed with a second adrenal crisis. Continuous intravenous administration of HC (100 mg·m⁻²·d⁻¹) was resumed. At 14 days of life, hyponatremia (134 mEq/L) and hyperkalemia (5.7 mEq/L) persisted despite the oral administration of sodium polystyrene sulfonate. Therefore, oral administration of FC at 0.2 mg/d and sodium chloride at 1.0 g/d was initiated. Hyperkalemia (6.6 mEq/L) and high ARC (462.7 pg/mL) did not improve. At 18 days of life, FC was increased to 0.4 mg/d. At 21 days of life, she gained weight, but hyperkalemia (6.4 mEq/L) and high ARC (372.3 pg/mL) persisted. We increased FC to 0.6 mg/d and changed a regular formula to a low-potassium and high-sodium formula. Subsequently, hyponatremia and hyperkalemia improved. A blood test at 25 days of life showed that ARC tended to decline but was still high (206.2 pg/mL). During the course of treatment, the patient showed no significant changes in blood pressure or heart rate. At 33 days of life, ARC decreased to 0.6 pg/mL. We started to gradually reduce FC dosage, which reached to 0.1 mg/d at 3 months of age. Hyponatremia and hyperkalemia did not recur when the low-potassium and high-sodium formulas were discontinued and ARC remained low (0.6 pg/mL). After 7 months, the patient had no recurrence of electrolyte abnormalities or adrenal crisis.

Since birth, she had no symptoms suggestive of urinary tract infection. At 22 days of life, repeated ultrasonography showed no kidney or urethral malformation. Secondary pseudoaldosteronism was unlikely.

After obtaining informed consent from her parents, we extracted the genomic DNA from peripheral blood samples of the patient and her parents. Sanger sequencing of *CYP21A2* (NM_000500.9) suggested that: i) her mother had a heterozygous c.293-13C>G variant, ii) her father had on the same allele both c.1069C>T (p.Arg357Trp variant) and the deletion encompassing c.293-13C, and iii) the proband was compound heterozygous for alleles with pathogenic alterations, individually transmitted by her parents (**Fig. 2**). These two nucleotide substitutions are pathogenic variants (5). Exome sequencing of the proband revealed no pathogenic variants in the *NR3C2*, *SCNN1A*, *SCNN1B*, or *SCNN1G* genes associated with pseudohypoaldosteronism.

Discussion

In our patient with 21OHD, the high potassium levels were not controlled by administration of FC at 0.4 mg/d dose for 3 days but normalized with 0.6 mg/d FC and a low-potassium and high-sodium formula. We

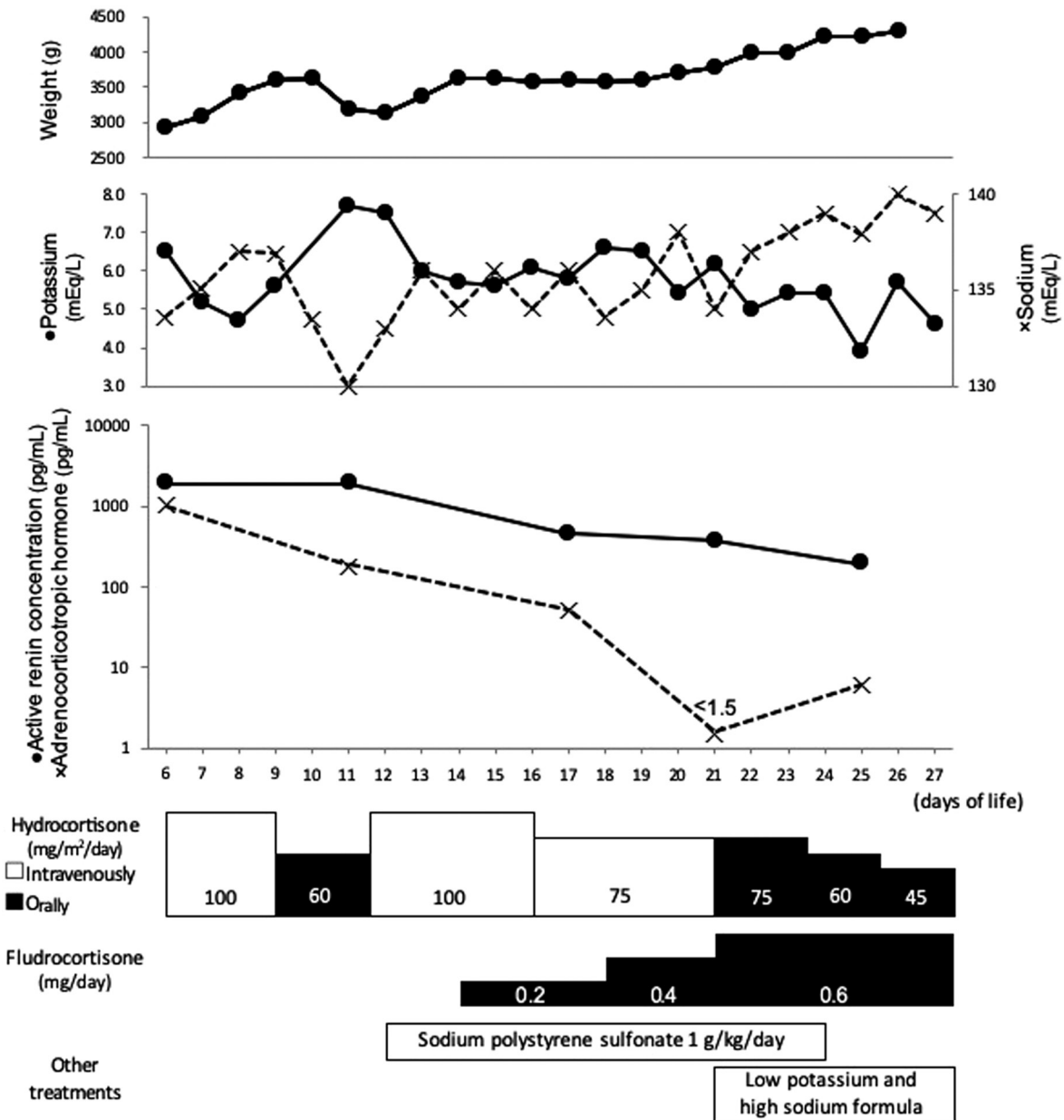


Fig. 1. Clinical course of the patients. Weights, blood test results, and treatments are shown. At 6 days of life, our patient had adrenal crisis. Serum potassium levels and active renin concentration remained high even with 0.4 mg/d of FC, and became normal with 0.6 mg/d of FC and a low-potassium and high-sodium formula.

considered that observation for 3 days was sufficient for evaluation of the treatment, as intravenous HC immediately shows mineralocorticoid activity. To the best of our knowledge, this is the first report of a neonate with 21OHD requiring > 0.4 mg/d of FC.

Hyperkalemia at 6 days of life might, at least in part, be attributed to a low glomerular filtration rate because the serum potassium level was normalized with decreased serum creatinine. In addition, we speculated that severe mineralocorticoid resistance was the reason why her hyperkalemia persisted even at 0.4 mg/d of FC. During administration of FC (0.4 mg/d), her sodium intake, except for the regular formula, was 9.6 mmol/kg/d, including oral sodium chloride, intravenous fluid therapy, and sodium polystyrene sulfonate. A high dosage

of sodium supplementation did not improve electrolyte imbalance in our patient (6). Her weight gain was good, and adrenocorticotrophic hormone levels normalized with oral administration of 60 mg/m²/d HC. These findings suggest that there was no intestinal malabsorption. Congenital and secondary pseudohypoaldosteronisms were excluded because there were no urinary tract infections or malformations and no pathogenic variants in the *NR3C2*, *SCNN1A*, *SCNN1B*, and *SCNN1G* genes. Because the patient had relatively common pathogenic alterations in the *CYP21A2* gene, the *CYP21A2* genotype could not explain her atypical phenotype. During her clinical course, her severe mineralocorticoid resistance gradually improved after 33 days of life. In a previous study, the expression of mineralocorticoid receptors

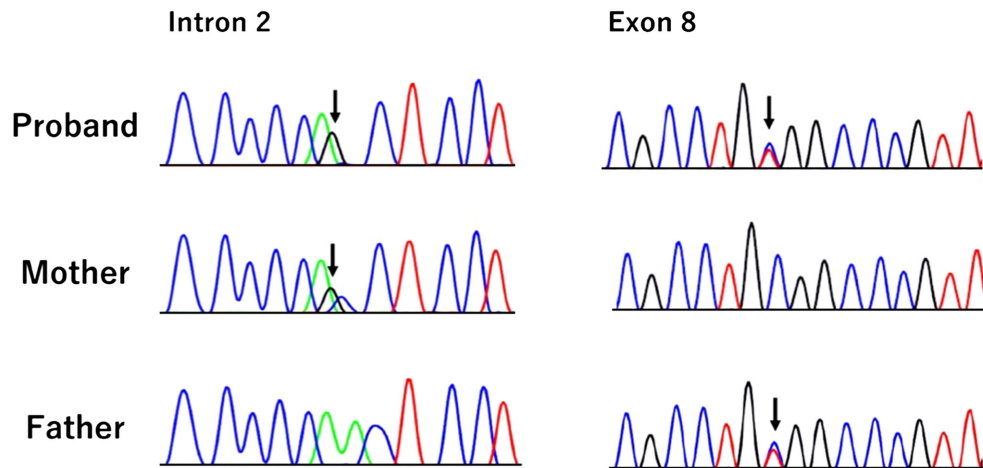


Fig. 2. Partial sequence of the intron 2 and exon 8 of *CYP21A2*. The upper panel shows a chromatogram of the proband harboring a hemizygous or homozygous c.293-13C>G and a heterozygous c.1069C>T (p.Arg357Trp). The middle panel shows a chromatogram of her mother harboring the heterozygous c.293-13C>G. The lower panel shows the chromatogram of her father harboring the heterozygous c.1069C>T and hemizygous or homozygous c.293-13C>A.

(MRs) in the distal nephron was low during the perinatal period and increased progressively after birth (7). In another study, hypovolemia induced dephosphorylation of MR in intercalated cells of the collecting duct, resulting in suppression of potassium excretion by aldosterone (8). Our patient may still have hypovolemia at 0.2 mg/d of FC because of no weight gain and high ARC. The effects of hypovolemia persisted for several days. Although the exact mechanism of mineralocorticoid resistance remains unclear, the combination of physiological and pathological compromises in MR expression can be related to transiently severe mineralocorticoid resistance in our patient.

We were unable to determine the cause of the adrenal crisis at 11 days. We speculate that reducing the dosage of HC to $60 \text{ mg} \cdot \text{m}^{-2} \cdot \text{d}^{-1}$, changing from continuous intravenous infusion to oral administration, or both precipitated a second adrenal crisis. A previous study showed that serum cortisol concentrations widely fluctuated upon oral administration of HC but remained stable upon continuous intravenous infusion (9). This implied that in our patient, unstable glucocorticoid absorption upon oral administration could have resulted in unstable serum cortisol concentrations, which may have triggered adrenal crisis. Our patient had a clinical course similar to that of most 21OHD patients who developed clinical symptoms and metabolic imbalances, including hyponatremia and hyperkalemia, 1–2 weeks after birth (3,10). Thus, in newborns with suspected 21OHD, electrolyte imbalances and clinical symptoms should be closely monitored during the first two weeks of life.

Notably, our patient had only one atypical laboratory finding of highly elevated ARC before treatment initiation and 6 days after birth. A previous study examining 14 patients with 21OHD showed that the ARC concentration was 30–100 pg/mL in most patients and 150–160 pg/mL in a few patients (11). We

speculate that extremely high ARC levels might be an indicator of the requirement for high-dose FC.

Conclusion

We report the case of a female neonate with 21OHD who showed severe salt-wasting and required $>0.4 \text{ mg/d}$ of FC. The pathophysiology of the transient severe resistance to FC in this patient is unknown. Neonates with 21OHD may show severe salt-wasting and require $>0.4 \text{ mg/d}$ of FC. Even during the treatment of HC and FC, electrolyte imbalance in 21OHD may occur or worsen 1–2 weeks after birth.

Ethical statement: This study complied with all the relevant national regulations and institutional policies, was in accordance with the tenets of the Helsinki Declaration, and was approved by the Institutional Review Board at Keio University School of Medicine (Institutional Review Board number 20150104 and 20170130). Written informed consent was obtained from the patient's parents.

Conflict of interests: The funding organizations played no role in the study design, collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the report for publication.

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