A Boy with Adrenal Hypoplasia Congenita without External Genital Abnormalities

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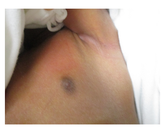
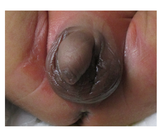
[Introduction]
Adrenal hypoplasia congenita (AHC) is a rare disorder with an estimated frequency of 1 case per 12,500 live births.
AHC causes 46,XY disorders in sex development (DSD) due to adrenal androgen deficiency.

[Objective]
Case report on a male AHC patient without external genital abnormalities.

[Case Report]
The baby was born at 37 weeks' gestation with a height of 46.5 cm (−0.49SD), a weight of 2,175 g (−1.57SD), and a head circumference of 30.0 cm (−1.93SD). He had generalized hyperpigmentation at birth. He was discharged without any problems five days after birth and required only phototherapy for a day. However, he was referred to a hospital at the age of 11 days due to poor feeding and poor weight gain. He was not thriving and had peripheral circulatory failure. Laboratory data showed hyponatremia (134 mEq/L) and hyperkalemia (7.1 mEq/L). It was suspected that he had adrenal insufficiency and was transferred to our hospital for closer investigation.

Clinical Characteristics upon Hospitalization

Height: 46.0 cm; Body weight: 2,060 g
Body temperature: 36.9˚C
Pulse rate: 140 beats/min; Systolic blood pressure: 72 mmHg
Anterior fontanelle: flat
Respiratory sound: clear
Heart sound: regular, no murmur
Skin: hyperpigmentation on whole body, especially on lips, areolas, external genitalia
External genitalia: complete male
Periphery: cold

Laboratory Data at Previous Hospital

Blood Count

WBC	13,6 00	/μL
Neut	39.6	%
Lymph	44.7	%
RBC	576×10⁴	/μL
Hb	19.4	g/dL
Ht	53.7	%
PLT	39.3×10⁴	/μL

Venous Blood Gas Analysis

pH	7.322	
pCO_2	57.0	mmHg
HCO_3^-	29.5	mmol/L
BE	1.6	mmol/L
AG	5.4	mmol/L
Lac	1.7	mg/dL
Glu	75	mg/dL

Biochemistry

TP	6.4	g/dL	BUN	9.1	mg/dL
Alb	4.2	g/dL	Cre	0.34	mg/dL
T-Bil	11.91	mg/dL	UA	3.9	mg/dL
AST	31	IU/L	Na	134	mEq/L
ALT	16	IU/L	K	7.1	mEq/L
LDH	357	IU/L	Cl	99	mEq/L
γ-GTP	137	IU/L	Ca	10.8	mg/dL
			IP	7.1	mg/dL
			CRP	0.11	mg/dL

after infusion → 136 mEq/L → 4.9 mEq/L

Gene Analysis (Sanger Sequencing)

no mutation in NR0B1

Adrenocorticosteroid Data (at 11 days old)

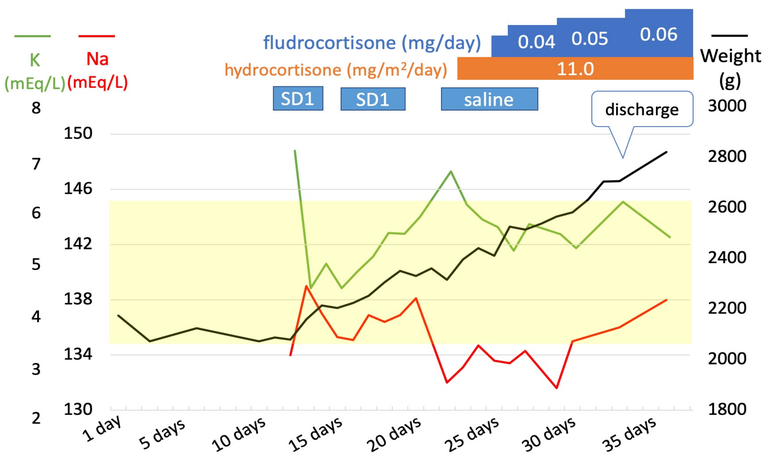
* 5 days ** 12 days *** 13 days

Glucocorticoid			
ACTH	1,078	pg/mL	(7.2-63.3)
Cortisol	5.1	μg/dL	(4.9-29.7)
17αOHP*	1.7	ng/mL	(< 5)
Mineralocorticoid			
Renin activity	187.9	ng/mL/hr	(7.403.74±SD)
Aldosterone	294.5	ng/dL	(52.19±23.49SD)
DOC**	0.33	ng/mL	(0.088±3.9SD)
Androgen			
DHEA-S	4.1	μg/dL	(5 days; 21.5±16.8SEM)
Testosterone***	55	ng/dL	(10-230)

GC-MS Measurements of Urinary Steroid Hormones (at 11 days old)

Metabolites of pregnenolone
P5: not detected; 21OHP5: low
Metabolites of 17αOHP
5,16Adien, 15,17diOHP5: low
Metabolites of DHEA
DHEA, AD5, 16αOHDHEA, 16βOHDHEA, 16oxoAD5, AT5: low
Metabolites of Androstenedione
An: high
→ Δ5 steroid decreased and androstenedione was maintained.

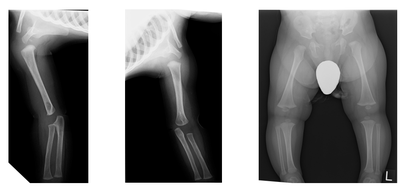
Clinical Course During Hospitalization



ACTH Test (at 21 days old)

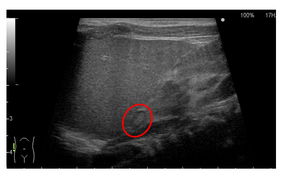
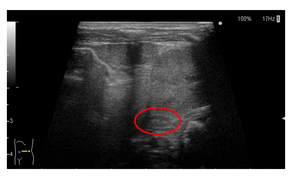
Tetracosactide acetate 0.25 mg/m² i.v.
Cortisol (base) 9.6 μg/dL
(peak) 8.2 μg/dL (> 15)
→ no response

X-ray (at 5 months old)



→ no obvious abnormalities

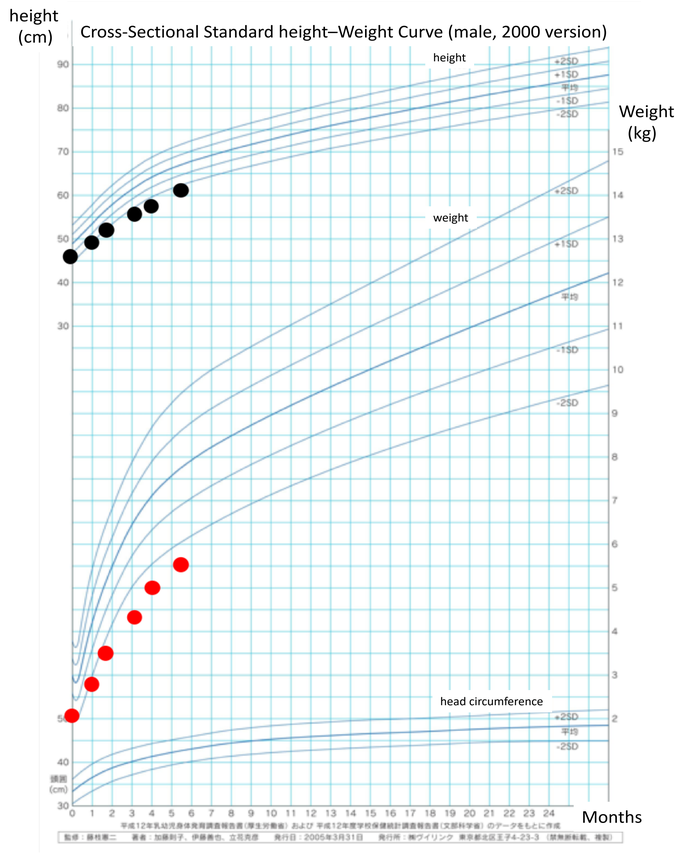
Ultrasonography (at 20 days old)

Adrenal glands (major axis): right 5 mm, left 6 mm
→Both are smaller than normal size.

Low serum and metabolites of steroids + small adrenal glands
→ diagnosis of AHC

Growth Curve to Date



[Discussion]

Importance of Early Diagnosis of AHC

- AHC often causes adrenal insufficiency during the neonatal period.[1)]
- However, AHC cannot be detected by neonatal mass screenings because 17OH-progesterone does not increase with AHC.

We suspected a decrease in adrenal function due to hyperpigmentation throughout the patient's body and examined his adrenal function. GC-MS measurements of urinary steroid hormones confirmed the diagnosis.

Progress of this Case

- Patient presented generalized hyperpigmentation at birth but no external genital abnormalities.
- Metabolites of Δ5 steroids were lower, but metabolites of androstenedione were normal at 11 days old.
- Adrenal insufficiency became apparent after the age of 20 days.

We believe that his fetal adrenal gland secreted sufficient androgens for external genital development; however, the development of his post-natal adrenal glands was impaired. A case of DAX-1 abnormality with high testosterone in early infancy has been reported.[2)] We suspected that this case was a DAX-1 abnormality, but we found no *NR0B1* mutation.

[Conclusions]
We encountered a case of AHC with no external genital abnormalities.
Hyper-pigmentation of the skin is an important sign of AHC even when there is no abnormality in the external genitalia.

[References] 1) Fujieda K. and Tajima T. Pediatr Res. 57: 62R, 2005 2) Ge J. et al. World J Pediatr 15: 309, 2019

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Adrenals and HPA Axis
Ikumi Umeki
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