A case of ACTH resistance with generalized hyperpigmentation at birth

Sasaki Takako1, Amano Naoko2, Narumi Satoshi2, Hasegawa Tomonobu2, Tomita Mai1,2, Okada Junichiro2, Hisano Tadashi3, Yatsuga Shuichi1, Koga Yasutoshi1
1) Department of Pediatrics and Child Health, Kurume University School of Medicine, Japan
2) Department of Pediatrics, School of Medicine, Keio University, Japan
3) Department of neonatal care unit, St Mary’s Hospital, Japan

1. Introduction

Cholesterol becomes pregnenolone. The MC2R gene (MC2R) encodes the receptor for ACTH, and MC2R mutations cause ACTH resistance. We describe a MC2R mutation-carrying ACTH resistance patient, who exhibited generalized hyperpigmentation at birth.

\[
\begin{align*}
\text{opiomelanocortin} & \rightarrow \text{ACTH} \\
\text{yMSH} & \rightarrow \text{ACTH} \\
\beta \text{lipotropin} & \rightarrow \text{ACTH}
\end{align*}
\]

A cytochrome P450sec (P450) converts cholesterol into pregnenolone, which is then converted into cortisol by the steroidogenic acute regulatory protein (StAR).

ACTH: adrenocorticotropic hormone, MC2R: Melanocortin 2 receptor, MRAP: melanocortin 2 receptor accessory protein, StAR: steroidogenic acute regulatory protein, MSH: melanocyte-stimulating hormone

2. Case Report

0 day of age, male
birth at 37 week of gestation
birth height 48 cm (+0.10 SD)
birth weight 2,112 g (-0.64 SD)

BT 35.9 C, BP mean 25 mmHg,
HR 70 /min, RR 70/min, SpO2 99% (O2 3L)
Apgar score: 4/7
(Appearance 0/0 Pulse 2/2, Grimace 1/2, Activity 0/1, and Respiration 1/2)

generalized hyperpigmentation (especially armpit, penis, micropenis (stretched penile length, 18 mm), testis palpable
pH 7.135, PaCO2 58.7 mmHg, HCO3 - 18.9 mmol/L
BE -11.2 mmol/L, Lac 7.7 mmol/L, AG 13.2meq/L

Na 136 mEq/L, renin activity 100 ng/kg/h,
K 4.6 mEq/L, aldosterone 1.6 pg/dl,
Cl 104.7 mEq/L, LH <0.1 mIU/L,
ACTH 27.19 pg/dl, FSH 0.46 mIU/L
cortisol 1.4 μg/dl,

<steroid profile in urine>
Cortisol, and aldosterone metabolites: within normal range
17OHPI metabolites: slightly high level

<chromosome> 46,XY
<abdominal CT> normal size of adrenal gland
<head MRI> normal size of pituitary

An artificial respirator was needed because of dyspnea, acidemia, and low blood pressure, and dopamine (0.05y) was injected. Primary adrenal insufficiency was suspected due to the physical findings, and glucocorticoid was administered at birth.

His general condition improved, and respirator was turned off at 5 days of age.

3. Methods & Results

Methods: Known genes associated with primary adrenal insufficiency were screened with use of next-generation targeted sequencing. The identified MC2R mutations were validated by conventional PCR-based sequencing.

Results:
(previously reported in patients with ACTH resistance)

4. Discussion

There are many causes of adrenal insufficiency in neonates, such as congenital adrenal hyperplasia, X-linked congenital adrenal hypoplasia, and 21-Hydroxylase deficiency. Adrenal insufficiency occurred at birth in this case. Normal serum electrolytes, and serum aldosterone level were normal. Serum cortisol level was low, and serum ACTH level was high, indicating ACTH resistance caused by MC2R mutations.

MC2R mutations have been described as having common episodes, such as seizure, hypoglycemia, severe infection, and tall stature/failure to thrive. The patients’ height is related to MC2R mutations and ACTH level.

Some MC2R mutation cases were treated as adrenal hypoplasia. They were treated with unnecessary hydrocortisone.

This case was treated with hydrocortisone (~15 mg/m²/day), there are no common episodes and he does not have tall stature (~1.3 SD at 18 months).

Appropriate diagnosis is important for MC2R mutation.

5. Conclusion

A neonate presenting symptoms suggesting adrenal insufficiency and/or hyperpigmentation should be considered as an MC2R mutation.

References: (1) Elia, et al. Clin Endocrinol 2000,