
# Congenital Hypoaldosteronism of Unknown Etiology in Five Half-Siblings

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## Background

- All 5 Caucasian half-siblings of 1 mother and 3 unrelated fathers have congenital hypoaldosteronism
- 21-hydroxylase screening, serum glucoses, and blood pressures all normal
- Females had no virilization
- Mother had normal puberty; no history of salt wasting, electrolyte disturbance, or blood pressure abnormality
- All fathers reported as healthy
- No known family history

## Objective

- To determine the etiology of congenital hypoaldosteronism in this family.

## Hypothesis

- The etiology is a rare genetic disorder transmitted by the mother.

## Methods

- All siblings – daily mineralocorticoid therapy, prn stress steroid therapy
- Sibling 1 – started cortisol replacement therapy by neonatology, weaned off by endocrinology
- Diagnostic studies summarized in table
- University of Iowa Hospitals & Clinics (UIHC) genetics evaluation – after sibling 2 (father B) was born
- National Institutes of Health (NIH) evaluation – mother & siblings 1, 2, and 4 (fathers A, B, and C)
  - Endocrinology, genetics, and nephrology

## Results

- UIHC and NIH evaluations – inconclusive
- Mother's evaluation – not consistent with hypoaldosteronism or any adrenal insufficiency
- Normal chromosome microarray analysis – mother, siblings 1 and 2
- Siblings 1 and 2 *CYP11B1* gene sequencing unremarkable; sibling 2 *CYP11B2* gene sequencing pending
- Hypoaldosteronism at level of the kidney ruled out
- Non-isolated mineralocorticoid deficiency (evidence of impaired cortisol synthesis)
  - Elevated ACTH levels
  - Abnormal stimulated cortisol levels
  - Requirements for stress steroid coverage
- Good response to mineralocorticoid therapy
- Normal growth patterns
- Etiology still unknown

| Sibling | Initial Laboratory Studies | ACTH Stimulation Testing | Other Testing & Comments |
|---|---|---|---|
| **1**<br>Female<br>Age 12<br>Father A | Day 1 of life:<br>Sodium 131 mEq/L<br>Potassium 5.9 - 10.5 mEq/L (ventricular tachycardia on day 4)<br>Cortisol 14 mcg/dL<br>Androstenedione 793 ng/dL<br>11-desoxycortisol 1979 ng/dL<br>Testosterone 65 ng/dL<br>Other adrenal hormones unremarkable<br>ACTH 245 pg/mL | **Cortisol**<br>On fludrocortisone:<br>10 → 10 mcg/dL<br>QNS → 15 mcg/dL<br>17 → 16 mcg/dL<br>11 → 11 mcg/dL<br>Off fludrocortisone:<br>9.7 → 10.3 mcg/dL<br>5 → 8.3 mcg/dL<br>12.9 → 14 mcg/dL<br>9.9 → 16 mcg/dL<br>Other adrenal hormones unremarkable | • Started hydrocortisone per neonatology (34 wks gestation) before renin & aldosterone drawn; weaned off by endocrinology<br>• Initially considered 11-hydroxylase deficiency - not entirely consistent<br>• Chromosomes and microarray normal<br>• MRI – normal adrenal glands<br>• *CYP11B1* gene sequencing unremarkable<br>• Stimulated cortisol levels did not rise normally<br>• Observed adrenal crises<br>• Mild hyponatremia, hyperkalemia, & low aldosterone when briefly off fludrocortisone<br>• Aldosterone < 4 ng/dL off fludrocortisone<br>• Renin 10 ng/mL/hr off fludrocortisone<br>• ACTH as high as 300 pg/mL |
| **2**<br>Male<br>Age 8<br>Father B | Day 16 of life:<br>Sodium 125 mEq/L<br>Potassium 6.9 mEq/L<br>CO2 19 mEq/L<br>Cortisol 9.5 mcg/dL<br>11-desoxycortisol 723 ng/dL<br>Other adrenal hormones unremarkable<br>Aldosterone 19 ng/dL<br>Renin 35.88 ng/mL/hr | **Cortisol**<br>On fludrocortisone:<br>13 → 16 mcg/dL<br>Off fludrocortisone:<br>14.1 → 18.7 mcg/dL<br>Corticosterone:<br>374 → 1140 ng/dL<br>18-OH corticosterone:<br>7.9 → 11 ng/dL<br>Other adrenal hormones unremarkable | • Initially considered 18-hydroxylase deficiency<br>• Chromosomes and microarray normal<br>• Stimulated cortisol levels did not rise normally<br>• 18-OH corticosterone/aldosterone <10 (suspicious for corticosterone methyloxidase type I deficiency)<br>• *CYP11B1* gene sequencing unremarkable<br>• Renin 3.7 ng/mL/hr off fludrocortisone<br>• Aldosterone < 8 ng/dL off fludrocortisone<br>• ACTH as high as 114 pg/mL |
| **3**<br>Female<br>Father C | Day 8 of life:<br>Sodium 120 mEq/L<br>Potassium 8.1 mEq/L<br>CO2 10 mEq/L<br>Cortisol 88 mcg/dL<br>Other adrenal hormones unremarkable<br>Aldosterone 9.1 ng/dL<br>ACTH 803 pg/mL | | • Mother on glucocorticoid early in pregnancy<br>• Amniocentesis – no evidence of 21-hydroxylase deficiency<br>• Died @ 12 months during acute gastroenteritis. Cause of death – metabolic acidosis, hyperkalemia, hyponatremia, & hypoglycemia |
| **4**<br>Male<br>Age 4<br>Father C | Day 4 of life:<br>Sodium 134 → 128 mEq/L<br>Potassium 6.2 → 8.4 mEq/L<br>Cortisol 4.8 mcg/dL<br>Other adrenal hormones unremarkable<br>Aldosterone 21 ng/dL<br>ACTH 169 pg/mL | **Cortisol**<br>On fludrocortisone:<br>14 → 39 mcg/dL<br>Other adrenal hormones unremarkable | • Renin as high as 13 ng/mL/hr (suspected missed doses)<br>• ACTH as high as 537 pg/mL |
| **5**<br>Male<br>Age 1<br>Father C | Day 3 of life:<br>Sodium 140 mEq/L<br>Potassium 5.3 mEq/L<br>4 weeks old, on fludrocortisone:<br>Renin 12 ng/dL<br>Aldosterone 66 ng/dL<br>ACTH 76 pg/mL | | • Fludrocortisone started at 3 days of life due to family hx<br>• 3 months old, on fludrocortisone:<br>– Cortisol 7.9 mcg/dL<br>– DHEA 458 ng/dL<br>–17-OH pregnenolone 1223 ng/dL<br>– Other adrenal hormones unremarkable<br>• ACTH as high as 76 pg/mL<br>• Hyponatremia occurs with single missed dose |

Orange = elevated level; blue = low level.

## Conclusion

### Diagnosis

Hyperreninemic hypoaldosteronism and partial adrenal insufficiency

### Differential

- **Autosomal recessive disorder of aldosterone synthesis** extremely unlikely
  - Misassigned paternity ruled out
  - Siblings have impaired cortisol synthesis, which is generally not present
  - Sibling 2 *CYP11B2* pending
- **Autosomal recessive disorder unlinked to the aldosterone synthase gene** unlikely
  - Described in literature but not among half-siblings
- **De novo autosomal dominant mutation in the mother** unlikely
  - 50% chance of inheritance
  - No cases described in literature
- **X-linked recessive conditions** unlikely
  - X-inactivation skewing necessary for both females to be affected
  - Congenital adrenal hypoplasia mainly affects males; no phenotypic features in the males
  - Perinatal adrenoleukodystrophy (ADL) rare; neonatal ADL associated with neurologic disease
- **Mitochondrial disease** most likely etiology
  - No cases described in literature
  - Mitochondrial DNA mutation in mother with variation in ova leading to variable disease severity
  - Planned evaluation: Plasma and urine amino acids, urine organic acids, lactic acid, and pyruvate; if abnormal → screen for mitochondrial DNA mutations

**References**

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