Novel Cases of Congenital Hyperreninemic Hypaldosteronism
Jan M. Foote

DISCLOSURES

✓ I have no actual or potential conflicts of interest in relation to this presentation.
✓ I will not discuss any “off label” or investigational uses in my presentation.

Objectives

1. Identify the main actions of aldosterone
2. Discuss the causes of hypoaldosteronism
3. 0.1% of hypaldosteronism

Case Studies
Aldosterone

- Steroid hormone (mineralocorticoid)
- Produced by zona glomerulosa of adrenal cortex
- Synthesized from corticosterone
- Regulated by:
  - Renin-angiotensin system
  - Plasma potassium concentration
  - Adrenocorticotropic hormone

Aldosterone Actions

- Regulate blood pressure
- Increase the retention of sodium and water
- Increase the excretion of potassium

Hyperaldosteronism

- Hypertension
- Headache
- Blurred vision
- Hypokalemia
- Fatigue
- Muscle cramps
- Muscle weakness
- Numbness
- Temporary paralysis
- Hypernatremia
- Polydipsia
- Metabolic alkalosis
Hypoaldosteronism

- Hypotension
- Hyponatremia
- Hyperkalemia
- Metabolic acidosis
- Weight loss
- Salt craving
- Dizziness
- GI disturbances
- Palpitations

Hypoaldosteronism Causes

- Hyporeninemic hypoaldosteronism ↓R • ↓A • nl C
- Diabetic nephropathy
- Chronic interstitial nephritis
- NSAID, ACE-I, ARB, cyclosporine
- HIV
- Primary aldosterone deficiency
- Addison's disease ↑R • ↓A • ↓C
- Congenital adrenal hyperplasia ↑R • ↓A • ↓C
- Aldosterone synthase deficiency ↑R • ↓A • nl C
- Heparin use ↑R • ↓A • nl C
- Aldosterone resistance
- K+ sparing diuretics (aldosterone antagonists)
- Pseudohypoaldosteronism ↑R • ↑A • nl C

Hypoaldosteronism Treatment

- Treatment varies with the etiology of hypoaldosteronism
- Fludrocortisone
- Sodium chloride in infants
- Liberalization of salt intake
- Glucocorticoids if cortisol deficient
- Normal saline for hypovolemia
- Correct for metabolic acidosis
## Congenital Hypoaldosteronism

<table>
<thead>
<tr>
<th>Five Caucasian Half-Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>o One mother</td>
</tr>
<tr>
<td>o Three unrelated fathers</td>
</tr>
<tr>
<td>o 21-hydroxylase screening, serum glucose, and blood pressures normal</td>
</tr>
<tr>
<td>o Females – no virilization</td>
</tr>
<tr>
<td>o Mother – normal puberty; no history of salt wasting, electrolyte disturbance, or blood pressure abnormality</td>
</tr>
<tr>
<td>o All fathers healthy</td>
</tr>
<tr>
<td>o No family history of adrenal problems</td>
</tr>
</tbody>
</table>

### Sibling 1: Female

**Father A**

- Started on hydrocortisone by neonatology
- Initially considered 11-hydroxylase deficiency
- Chromosomes & CMA normal
- MRI – normal adrenal glands
- CYP11B1 gene sequencing normal
- Stimulated cortisol - no rise x 7, partial response x 1
- 18-OH corticosterone/aldosterone ratio normal
- Observed adrenal crisis
- Off fludrocortisone briefly: ↓Na+, ↑K+
  - Aldosterone <4 ng/dL
  - Renin 10 ng/mL/hr
  - ACTH 300 pg/mL

### Sibling 2: Male

**Father B**

- Initially considered 18-hydroxylase deficiency
- Chromosomes & CMA normal
- CYP11B1 gene sequencing normal
- Stimulated cortisol – no rise x 2
- 18-OH corticosterone/aldosterone <10 (suspicious for CMO type 1 deficiency)
- Off fludrocortisone briefly: Albminosterone <4 ng/dL
  - Renin 3.7 ng/mL/hr
  - ACTH 114 pg/mL
<table>
<thead>
<tr>
<th>Sibling 3: Female</th>
<th>Father C</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Day 8 of life:</td>
<td>• Mother on glucocorticoid during pregnancy</td>
</tr>
<tr>
<td>Sodium 120 mEq/L</td>
<td>• Amniocentesis – no evidence of 21-</td>
</tr>
<tr>
<td>Potassium 8.1 mEq/L</td>
<td>hydroxylase deficiency</td>
</tr>
<tr>
<td>CO₂ 10 mEq/L</td>
<td>• Died at 12 months during acute</td>
</tr>
<tr>
<td>• Cortisol 8.8 mcg/dL</td>
<td>gastroenteritis – metabolic acidosis,</td>
</tr>
<tr>
<td>Other adrenal hormones normal</td>
<td>hyperkalemia, hyponatremia, &amp;</td>
</tr>
<tr>
<td>• Aldosterone 9.1 ng/dL</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>ACTH 803 pg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sibling 4: Male</th>
<th>Father C</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Day 4 of life:</td>
<td>• Stimulated cortisol response normal</td>
</tr>
<tr>
<td>Sodium 134 → 128 mEq/L</td>
<td>• Renin 13 ng/ml/hr (suspected missed</td>
</tr>
<tr>
<td>Potassium 6.2 → 8.4 mEq/L</td>
<td>doses of fludrocortisone)</td>
</tr>
<tr>
<td>• Cortisol 4.8 mcg/dL</td>
<td>• ACTH 537 pg/mL</td>
</tr>
<tr>
<td>Other adrenal hormones unremarkable</td>
<td></td>
</tr>
<tr>
<td>• Aldosterone 21 ng/dL</td>
<td></td>
</tr>
<tr>
<td>• ACTH 169 pg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sibling 5: Male</th>
<th>Father C</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Day 3 of life:</td>
<td>• Fludrocortisone started on day 3 of</td>
</tr>
<tr>
<td>Sodium 140 mEq/L</td>
<td>life due to family history</td>
</tr>
<tr>
<td>Potassium 5.3 mEq/L</td>
<td>• 3 months old, on fludrocortisone:</td>
</tr>
<tr>
<td>4 weeks old, on fludrocortisone:</td>
<td>Cortisol 7.9 mcg/dL</td>
</tr>
<tr>
<td>Renin 12 ng/dL</td>
<td>DHEA 458 ng/dL</td>
</tr>
<tr>
<td>Aldosterone 66 ng/dL</td>
<td>17-OH pregnenolone 1223 ng/dL</td>
</tr>
<tr>
<td>ACTH 76 pg/mL</td>
<td>Other adrenal hormones</td>
</tr>
<tr>
<td></td>
<td>unremarkable</td>
</tr>
<tr>
<td></td>
<td>• ↓Na+ occurs with every single missed</td>
</tr>
<tr>
<td></td>
<td>dose</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>
All siblings treated with fludrocortisone & stress steroid coverage
• Evaluated by U of Iowa Genetics
• Evaluated at National Institutes of Health
  - Endocrinology, genetics, nephrology
• Mother’s evaluation – not consistent with hypoaldosteronism or any adrenal insufficiency; normal chromosomes & CMA
• Non-isolated mineralocorticoid deficiency
  - Evidence of impaired cortisol synthesis
    • Elevated ACTH levels, abnormal stimulated cortisol levels, requirements for stress steroid coverage
• Normal growth patterns
• ETIOLOGY of HYPOALDOSTERONISM STILL UNKNOWN

Hyperreninemic Hypoaldosteronism with Partial Adrenal Insufficiency

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

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

DIFFERENTIAL DIAGNOSES
Autosomal recessive disorder of aldosterone synthesis extremely unlikely
  - Misassigned paternity ruled out
  - Impaired cortisol synthesis – generally not present
  - Sibling 2 – CYP11B2 pending
Autosomal recessive disorder unlinked to the aldosterone synthase gene unlikely
  - Described in literature – not in half-siblings
De novo autosomal dominant mutation in the mother unlikely
  - 50% chance of inheritance
  - No cases described in literature
DIFFERENTIAL DIAGNOSES

» X-linked recessive conditions unlikely
» Congenital adrenal hypoplasia mainly affects males; no phenotypic features in these males
» Neonatal adrenoleukodystrophy rare; associated with neurologic disease
» Mitochondrial disease?
» No cases described in literature
» Mitochondrial DNA mutation in mother with variation in ova leading to variable disease severity
» Sibling 2 – plasma & urine amino acids, urine organic acids, lactic acid, & pyruvate normal
» If abnormal, would have screened for mitochondrial DNA mutations

DIFFERENTIAL DIAGNOSES

Discussion...

Special thanks to Carol Van Ryzin & NIH for assistance in evaluating this family.

References


Young, W. F. (2013). Etiology, diagnosis, and treatment of hypoaldosteronism (type 4 RTA). In UpToDate, R. H. Sterns & A. Lacroix (Eds.). Waltham, MA: UpToDate.