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Novel Cases of Congenital Hyperreninemic Hypaldosteronism

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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 aldosterone

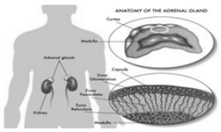
2 Discuss the causes of hypoaldosteronism

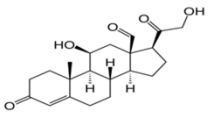
3 Dis… of hy… …nism

Case Studies

Aldosterone

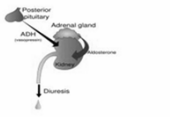
- ✓ Steroid hormone (mineralocorticoid)
- ✓ Produced by zona glomerulosa of adrenal cortex
- ✓ Synthesized from corticosterone
- ✓ Regulated by:
  - ✓ Renin-angiotensin system
  - ✓ Plasma potassium concentration
  - ✓ Adrenocorticotropic hormone





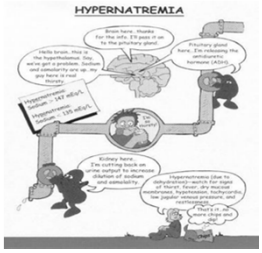
Aldosterone Actions

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



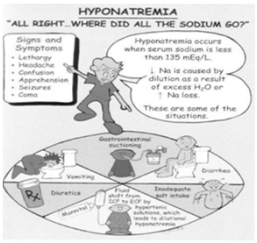
Hyperaldosteronism

- ✓ 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

R = Renin
A = Aldosterone
C = Cortisol

- ✓ 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

Five Caucasian Half-Siblings

- One mother
- Three unrelated fathers
- 21-hydroxylase screening, serum glucoses, and blood pressures normal
- Females – no virilization
- Mother – normal puberty; no history of salt wasting, electrolyte disturbance, or blood pressure abnormality
- All fathers healthy
- No family history of adrenal problems

Sibling 1: Female

- Day 1 of life:
  Sodium 131 mEq/L
  Potassium 5.9-10.5 mEq/L
  (ventricular tachycardia day 4)
- Cortisol 14 mcg/dL
  Androstenedione 793 ng/dL
  11-desoxycortisol 1979 ng/dL
  Testosterone 65 ng/dL
- ACTH 245 pg/mL

☐ Low
☐ High

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

- Day 16 of life:
  Sodium 125 mEq/L
  Potassium 6.9 mEq/L
  CO_2 19 mEq/L
- Cortisol 9.5 mcg/dL
  11-desoxycortisol 723 ng/dL
- Aldosterone 19 ng/dL
  Renin 36 ng/mL/hr

☐ Low
☐ High

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:
  Aldosterone <4 ng/dL
  Renin 3.7 ng/mL/hr
  ACTH 114 pg/mL

Sibling 3: Female

- Day 8 of life:
  Sodium 120 mEq/L
  Potassium 8.1 mEq/L
  CO_2 10 mEq/L
- Cortisol 8.8 mcg/dL
  Other adrenal hormones normal
- Aldosterone 9.1 ng/dL
  ACTH 803 pg/mL

☐ Low
☐ High

Father C

- Mother on glucocorticoid during pregnancy
- Amniocentesis – no evidence of 21-hydroxylase deficiency
- Died at 12 months during acute gastroenteritis – metabolic acidosis, hyperkalemia, hyponatremia, & hypoglycemia

Sibling 4: Male

- Day 4 of life:
  Sodium 134 → 128 mEq/L
  Potassium 6.2 → 8.4 mEq/L
- Cortisol 4.8 mcg/dL
  Other adrenal hormones unremarkable
- Aldosterone 21 ng/dL
- ACTH 169 pg/mL

☐ Low
☐ High

Father C

- Stimulated cortisol response normal
- Renin 13 ng/ml/hr (suspected missed doses of fludrocortisone)
- ACTH 537 pg/mL

Sibling 5: Male

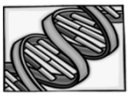
- Day 3 of life:
  Sodium 140 mEq/L
  Potassium 5.3 mEq/L
- 4 weeks old, on fludrocortisone:
  Renin 12 ng/L
  Aldosterone 66 ng/dL
  ACTH 76 pg/mL

☐ Low
☐ High

Father C

- Fludrocortisone started on day 3 of life due to family history
- 3 months old, on fludrocortisone:
  Cortisol 7.9 mcg/dL
  DHEA 458 ng/dL
  17-OH pregnenolone 1223 ng/dL
  Other adrenal hormones unremarkable
- ↓Na+ occurs with every single missed dose

Summary



- 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.

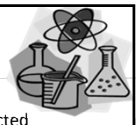
HYPOTHESIS

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
  - X-inactivation skewing necessary for both females to be affected
  - 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

? Discussion…

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

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