Congenital Hypoaldosteronism of Unknown Etiology in Five Half-Siblings

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No disclosures.

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
- NIH 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 unrewardable; 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

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 linked 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 hyperplasia mainly affects males; no phenotypic features in the males
  - Perinatal adrenal insufficiency (ADH) rare; neonatal ADH 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, uric acid, organic acids, lactic acid, and pyruvate; if abnormal screen for mitochondrial DNA mutations

Conclusions

References

Acknowledgments
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Table

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| 1 Female | Age 12 | Father A | Day 1 of life: Sodium 131 mEq/L, Potassium 3.9 - 10.5 mEq/L, centrilobular tachysarcardia on day 4. | Cortisol On fludrocortisone: 10 - 16 mcg/dL, DHEA 5 - 18 mcg/dL, Aldosterone < 8 ng/dL, ACTH 45 pg/mL. | Started hydrocortisone per neonatology (34 wks gestation) before renin & aldosterone drawn; weaned off by endocrinology.

| 2 Male | Age 14 | Father B | Day 16 of life: Sodium 129 mEq/L, Potassium 4.5 mEq/L, CO2 18 mEq/L. | Cortisol On fludrocortisone: 13 - 16 mcg/dL. | Initially considered 11-hydroxylase deficiency - not entirely consistent.

| 3 Female | Age 1 | Father C | Day 8 of life: Sodium 125 mEq/L, Potassium 3.1 mEq/L, CO2 10 mEq/L. | Cortisol On fludrocortisone: 11 - 14 mcg/dL. | Mother on glucocorticoid early in pregnancy.

| 4 Male | Age 4 | Father D | Day 3 of life: Sodium 140 mEq/L, Potassium 3.4 mEq/L, 8 weeks old, on fludrocortisone. | Cortisol On fludrocortisone: 12 ng/dL. | Fludrocortisone started at 3 days of life due to family history.

| 5 Male | Age 1 | Father E | Day 3 of life: Sodium 140 mEq/L, Potassium 3.4 mEq/L, 8 weeks old, on fludrocortisone. | Cortisol On fludrocortisone: 7.9 mcg/dL. | Fludrocortisone started at 3 days of life due to family history.

Orange = elevated level; blue = low level.