15 year-old boy with syncope and polyuria
15 yo Caucasian boy presents with few syncopal and near-syncopal episodes with exercise

- Eval by cardiology → sinus bradycardia
- Has a history of a “salt-problem” since infancy; previously followed by Pediatric Endocrinology
  - Stopped taking medication 9 years ago
  - Likes salty foods
  - Urinates ~ 7 times daily
HPI continued...

- ROS
  - Nl appetite; craves salty foods
  - Denies fatigue, wt loss, syncope at rest, seizures, H/A, palpitations, skin changes
  - + polyuria, + polydipsia
  - Growth spurt with voice change at ~ age 13 yrs.

- Meds
  - None

- Allergies
  - None

- Physical Exam
  - Wt: 58 kg (25-50\textsuperscript{th}%), Ht: 170.4 (25-50\textsuperscript{th}%)
### Past Medical History

- **Birth Hx:**
  - Mother received terbutaline for premature labor @ 6 months gestation
  - Full term, NSVD, mild jaundice; BW: 7 lbs 2 oz (30\textsuperscript{th}%)  
    - Breastfed x 2wks
    - 2 week visit 6.5lbs; continued wt. loss despite good po, 8-10 wet diapers/day
  - Admitted to Comer age 6 weeks for FTT and abnormal electrolytes
Family History
- No consanguinity
- Maternal uncle w/ edema and brown urine tx w/ prednisone

Physical Exam
T 36.9  BP 77/39  HR 177  Lt: 53.5cm (10^{\text{th}}\%)
Wt: 3.03 kg (< 3rd\%)
  - Skin tented, nl pigmentation
  - Ant fontanelle flat
  - Stretched phallus length
  - 3.5 cm, nl descended testes

128 89 35
6.2 17 0.2
Newborn screen neg for CAH TFTs, UA, UGI nl per PMD
Differential Diagnosis

- **Adrenal**
  - Congenital Adrenal Hyperplasia
  - Aldosterone deficiency
  - Defects in Cholesterol Biosynthesis
  - Adrenal hypoplasia congenita
  - Bilateral adrenal hemorrhage

- **Renal**
  - Aldosterone resistance
    - Autosomal recessive/Autosomal dominant Pseudohypoaldosteronism type 1
    - Pseudohypoaldosteronism type 2
    - Transient PHA secondary to renal injury

- **Central**
  - CRH or ACTH deficiency or resistance
Results

ACTH 51 pg/mL (9-52)
Cortisol 38 mcg/dL

Aldosterone 1207 ng/dL (5-90)
Renin >5000 mcU/mL
Urine Aldo 25 mcg/18h (1-8 mcg/24h)

17-OHprogesterone: <120 ng/dL (36-763)

Renal U/S: mild dilated of right collecting system

Newborn screen neg for CAH
TFTs, UA, UGI nl per PMD

UA: S.G. 1.007
chem and micro neg
UNa 27 mEq/L  Cr 11.3 mg/dL
FeNa 0.37

UOP 5-6ml/kg/h
Results

- **ACTH stimulation:**

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<th>Baseline</th>
<th>1 hour</th>
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<tr>
<td>Aldosterone</td>
<td>1207</td>
<td>1506</td>
</tr>
<tr>
<td>Renin</td>
<td>&gt;5,000</td>
<td>&gt;30,000</td>
</tr>
<tr>
<td>Cortisol</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>17-OHP</td>
<td>&lt;120</td>
<td>310</td>
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</tbody>
</table>

- **Dx:** Pseudohypoaldosteronism
Clinical Course

- Began and Na supplementation and Florinef
- Continued polyuria with nl electrolytes
- Found not to have Na channel defect
- Added natural licorice-could not tolerate taste
- No endo follow-up for nearly 10 years
- Present day: Neurocardiogenic syncope exacerbated by hypovolemia vs cardiogenic causes
  - Aldo 39 (< 22), Renin 2.5 (1.4-2.4), NI BMP
  - Increase fluid/salt intake prior to exercise, consider Florinef
- *Glycyrrhiza glabra*-native to Asia and Mediterranean
- Genus name *Glycyrrhiza* (Gr. *Glykos* (sweet) + *rhiza* (root))
- Active ingredient: Glycyrrhizin
- Metabolites include glycyrrhetic acid and its analog Carbenoxolone

### Purported Medicinal Uses

<table>
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<th>Treatment of Addison’s disease</th>
<th>Peptic ulcers, dyspepsia</th>
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<td>Glycemic control in NIDDM</td>
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<td>Cough and asthma</td>
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<td>Hirsutism</td>
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<td>Memory improvement</td>
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</table>
Mechanism of Action

- Glycyrrhizic acid inhibits 11-β-hydroxysteroid dehydrogenase type 2 (Stewart et al 1989)
  - Creates clinical state similar to Apparent Mineralocorticoid Excess
  - as little as 700mg/day glycyrrhizic acid can cause Na retention

Stewart et al 1987
Carbenoxolone:

Glycyrrhizic acid:

Figure 1. The 11βHSD isoenzymes: (1) 11βHSD1 is a NADPH-dependent reductase (that converts inactive cortisone to active cortisol) and a dehydrogenase (that converts cortisol to cortisone), expressed in the liver, adipose, gonadal and central nervous system tissues. 11βHSD1 functions mostly as a reductase in intact cells and organs. (2) 11βHSD2 is a NAD-dependent dehydrogenase enzyme that is highly expressed in the kidney and colon.

Espínldola-Atunes D, Kater CE
Treatment in Pseudohypoaldosteronism

- Carbenoxolone may have a role in Pseudohypoaldosteronism

Arai et al. 1994
Renin-Aldosterone suppression in renal PHA but no response to carbenoxolone in multiorgan PHA

- Difference in response as compared with Arai et al may be age-related

Hanukoglu et al 1997
References


