Update on CAH Treatment, Monitoring, & Transitioning

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Disclosures

• Contracted Research
  – Novartis Pharmaceuticals
  – Strongbridge Biopharma
  – Millendo Pharmaceuticals

• Consultant
  – Laboratory Corporation of America
  – Corcept Therapeutics
  – Janssen Pharmaceuticals
  – Novartis Pharmaceuticals
  – Diurnal LTD
  – Alder BioPharmaceuticals
  – Spruce Biosciences
  – Strongbridge Biopharma
Enzyme Defects Causing CAH

Cholesterol

StAR CYP11A1

Pregnenolone → Progesterone

3βHSD2

17OH-Pregnenolone → 17OH-Progesterone

CYP17A1 POR

11-Deoxycorticosterone

CYP11B2

Aldosterone

CYP11B1

Cortisol

17OH-Progesterone → 11-Deoxycorticosterone

CYP21A2 POR

Androgens & Estrogens

HSD17B3, SRD5A2, CYP19A1

Dehydroepiandrosterone (DHEA)

CYP17A1 POR CYB5A

17OH-Pregnenolone

3βHSD2

11-Deoxy-corticosterone
Types of CAH

- **21-Hydroxylase Deficiency (CYP21A2, P450c21)**
  - Cortisol ± Aldosterone Deficiency + Androgen Excess
  - 1:15,000 Births; Nonclassic >1:1000, <10% Diagnosed

- **17-Hydroxylase Deficiency (CYP17A1, P450c17)**
  - Mineralocorticoid Excess, HTN, Sexual Infantilism

- **11-Hydroxylase Deficiency (CYP11B1, P450c11β)**
  - Mineralocorticoid Excess, HTN, Androgen Excess

- **3β-Hydroxysteroid Dehydrogenase Type 2**
  - Like 21OHD in Girls, Boys Undervirilized

- **P450-oxidoreductase (POR) Deficiency**

- **Lipoid Congenital Adrenal Hyperplasia (LCAH)**
  - Steroid Acute Regulatory (StAR) Protein
  - Cholesterol Side Chain Cleavage (CYP11A1, P450scc)
  - All Steroids Deficient; Nonclassic Form Like FGD
21-Hydroxylase Deficiency (21OHD)

**ACTH**

- Cholesterol
  - CYP11A1
  - STAR

Pregnenolone → Progesterone

**CYP11A1**

17-hydroxy-pregnenolone

**CYP17A1**

- 11-deoxy-corticosterone (CYP21A2)
- Corticosterone (CYP11B2)
- 18-hydroxy-corticosterone (CYP11B2)
- Aldosterone

**Renin/Ang-II**

- zona glomerulosa
- zona fasciculata
- zona reticularis

**Androgen Excess Variable Glucocorticoid & Mineralocorticoid Deficiency**

- Androstenedione
  - AKR1C3
  - Testosterone

- Dehydroepiandrosterone Sulfate
  - SULT2A1
Nonclassic 21OHD Presentations

• Children
  – Body Hair & Odor
  – Rapid Growth; Voice & Behavior Changes

• Adolescent Girls & Young Women
  – Facial Hair & Acne
  – Irregular Menstrual Periods
  – Infertility

• >90% Of Females Never Diagnosed
• >99.9% Of Males Never Diagnosed
21OHD Rx Goals: Children

- Prevent Adrenal Crisis
  - Hydrocortisone <17 mg/m^2/d TID-QID
- Maintain Volume Status
  - Fludrocortisone 0.1-0.4 mg/d + Salt
- Minimize Androgen Excess: ???
- Prevent Early Puberty: ?GnRHa
- Maximize Height: ?rhGH
- Nonclassic Similar, Less Treatment

Speiser et al 2010 JCEM 95: 4133
Time For A Reality Check

There Are Now More Adults With CAH Than Children
The Transition Process

- Start Early, Phase In Gradually
  - Demonstrates Self-Management Skills, Knowledge of ‘Why’ & Motivation
  - Parents Role Shifts to ‘Consultant’

- Healthcare System(s)
- Specific Conditions & Providers
- Huge Spectrum of Individuals
- In USA, This Rarely Happens
- For CAH, Will Not Happen Without Help
  - Cystic Fibrosis Centers vs CAH Care
21OHD Adults CaHASE & NIH

- High or Suppressed Androgens Common
- Obesity Common, One-Third All Groups
- MetS, Insulin Resistance Common
- Elevated BP Common Classic > NCAH
- Low BMD Common 37% Adults
- Poor QoL Metrics
- TART 30-50% Boys & Men
- Adult Rx: 17 mg/m² HC; Dex 0.35 mg; Prednisone 7.5 mg (1/3 Each)
- Adult NCAH: Same Rx! Even More Dex

Arlt et al 2010 JCEM 95:5110
Finkelstain et al 2012 JCEM 97: 4429
CAH Treatment Goals: Adults

• Replace the Adrenal Insufficiency
  – Daytime Glucocorticoid + Fludrocortisone
  – Adrenal Crises Uncommon in Adults

• Control the Androgen Excess
  – Compliance is the Key
  – Often Requires Extra or Odd Dosing

• Prevent and Detect Neoplasms

• Mitigate Consequences of Chronic Rx
  – Bones, CV Risk, Cognition, Etc
Men With 21OHD & Androgens

Hypothalamus

Pituitary

Adrenal

Testis

CRH

GnRH

ACTH

LH

Cortisol

DHEAS, Testosterone

Testosterone
Testicular Adrenal Rests - Sono
Adrenal Rests: Treatment

• High-Dose Glucocorticoids
  – Often Shrinks Rest Tissue
  – Variable Effect on Testosterone, Sperm
  – Side Effects of Long-Term Use

• Testis-Sparing Surgery
  – Improves Mass Effect
  – Little Benefit For Testosterone, Sperm

• Up To 3-4 Years’ Rx Intensification

• TART, FSH > 35 IU/L Poor Prognosis

Claahsen-van der Grinten et al 2007 JCEM 92:612
King et al 2016 Clin Endocrinol 84:830
Fertility: 21OHD Women

- High Androgens
- High Progesterone
- Anovulation
- Inadequate introitus
- Vaginal Stenosis/Restenosis
Pregnancy & Classic CAH

- Few Attempt Pregnancy (<25%)
- Pregnancy Rate Normal (>90%)
- Salt Wasting Less Likely to Attempt
- Suppress AM Progesterone <0.6 ng/mL
  - Chronic ‘Luteal Phase’ from Adrenal Prog
- Discuss Genotyping Partner
- Androgens & 17OHP Rise; Placenta Protects Fetus From Maternal Androgens
- Unilateral/Bilateral Adrenalectomy?

Lo et al 1999 JCEM 84:930
Casteràs et al 2009 Clin Endocrinol 70:833
Adrenal Rests After ADX

Crocker et al 2012 JCEM 97: E2084
Another Reason to Take Your Meds
Massive Adrenal Myelolipoma
Nonclassic 21OHD in Adults

- Ascertainment Rate Low
  - <15% Present For Infertility
- 83% Pregnant in 1 Year +/- Treatment
- High Rate of Miscarriage
  - 26% Without Rx, 6.5% With Hydrocortisone
  - Replacement Hydrocortisone, No Labs
- Gentyping: 70% Carry Classic CAH Allele
- Stress Dosing? If CST Cortisol <14 µg/dL
- Treat Based on Goals & Needs
- No Data For Infertility or TART in Men
  - Often Stop Rx After Puberty
Glucocorticoid Options

• Hydrocortisone
  – Generally Need 3 Doses of 5-10 mg
  – CANNOT Control AM ACTH With PM Hydrocortisone

• Prednisone: Once Daily Works Sometimes
  – More Side Effects, Unreliable At Small Doses
  – Prednisolone, Methylprednisolone More Reliable

• Dexamethasone: Effective, Toxic, Titration Hard

• Combination: Day Hydrocortisone, PM Other
  – 15/5 mg Hydrocortisone + 1 mg Prednisolone QHS
## Glucocorticoid Step Therapy

<table>
<thead>
<tr>
<th>Step</th>
<th>Drug(s)</th>
<th>Frequency</th>
<th>Total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydrocortisone</td>
<td>TID or BID</td>
<td>15-30 mg</td>
</tr>
<tr>
<td>2</td>
<td>Hydrocortisone</td>
<td>BID-TID</td>
<td>15-25 mg</td>
</tr>
<tr>
<td></td>
<td>+ Prednisolone</td>
<td>HS</td>
<td>1-2.5 mg</td>
</tr>
<tr>
<td></td>
<td>+ Dexamethasone</td>
<td>HS</td>
<td>0.1-0.375 mg</td>
</tr>
<tr>
<td>3</td>
<td>Prednisolone</td>
<td>BID or TID</td>
<td>5-15 mg</td>
</tr>
<tr>
<td>4</td>
<td>Dexamethasone</td>
<td>QD or BID</td>
<td>0.5-2 mg</td>
</tr>
<tr>
<td>Analyte</td>
<td>Physiology</td>
<td>Goals &amp; Comments</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------</td>
<td>---------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Plasma renin</td>
<td>Volume status</td>
<td>Low to normal unless hypertension</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>Mineralocorticoid</td>
<td>Goal is normal</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>Mineralocorticoid</td>
<td>Goal is normal</td>
<td></td>
</tr>
<tr>
<td>Testosterone (T)</td>
<td>Total androgens</td>
<td>Adrenal + gonadal</td>
<td></td>
</tr>
<tr>
<td>Androstenedione</td>
<td>Mostly adrenal</td>
<td>Assess with T</td>
<td></td>
</tr>
<tr>
<td>SHBG</td>
<td>T binding protein</td>
<td>Estrogen raises</td>
<td></td>
</tr>
<tr>
<td>DHEAS</td>
<td>Major adrenal</td>
<td>Should be low</td>
<td></td>
</tr>
<tr>
<td>17OHP</td>
<td>Highly variable</td>
<td>Should not be low</td>
<td></td>
</tr>
<tr>
<td>Analyte</td>
<td>Physiology</td>
<td>Goals &amp; Comments</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------</td>
<td>------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>Gonadal axis</td>
<td>Low if adrenal androgen excess</td>
<td></td>
</tr>
<tr>
<td>A’dione/T</td>
<td>Adrenal vs gonadal androgen</td>
<td>Should be &lt;0.5</td>
<td></td>
</tr>
<tr>
<td>Semen analysis</td>
<td>Fertility</td>
<td>Normal is ideal</td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>Adrenal &amp; corpus luteum</td>
<td>Normalize for fertility (&lt;0.6 ng/mL) during follicular phase</td>
<td></td>
</tr>
</tbody>
</table>
Ever Wonder What Happens to All That Prog & 17OHP??
Steroid Profiling
LC-MS/MS
21OHD: C$_{21}$-Steroids
# C$_{21}$-Steroid Pathways in 21OHD

## Table 1. Concentrations of C$_{21}$ Steroids (ng/dL) in Serum

<table>
<thead>
<tr>
<th></th>
<th>21OHD Patients (n = 21)</th>
<th>Controls (n = 21)</th>
<th>Fold</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>540 [251.5–1899]</td>
<td>245 [137–358.5]</td>
<td>2.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>16OHP</td>
<td>111 [15.5–551.5]</td>
<td>4 [0.5–7.5]</td>
<td>27.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>21dF</td>
<td>1130 [322–6355]</td>
<td>32 [22–68.5]</td>
<td>35.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>11OHP</td>
<td>0 [0–49]</td>
<td>0 [0–0]</td>
<td>a</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>11-Deoxy cortisol</td>
<td>11 [7–53.5]</td>
<td>58 [24–151]</td>
<td>0.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>24 [6.5–133]</td>
<td>295 [110.5–558]</td>
<td>0.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cortisol</td>
<td>2295 [429–4632]</td>
<td>10 395 [6660–12 450]</td>
<td>0.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cortisone</td>
<td>459 [110–1163]</td>
<td>2195 [1492–2666]</td>
<td>0.2</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Turcu et al 2015 JCEM 100:2283
More Steroid Pathways in 21OHD
### C₁₉-Steroid Pathways in 21OHD

<table>
<thead>
<tr>
<th>Steroid</th>
<th>21OHD (n = 38)</th>
<th>Controls (n = 38)</th>
<th>Fold</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>80 [38-162]</td>
<td>26 [12-309]</td>
<td>3.0</td>
<td>0.09</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>155 [72-390]</td>
<td>42 [22-63]</td>
<td>3.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>11OHT</td>
<td>59 [21-104]</td>
<td>15 [9-21]</td>
<td>4.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>11KT</td>
<td>171 [105-366]</td>
<td>50 [29-78]</td>
<td>3.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>11OHA</td>
<td>351 [188-792]</td>
<td>118 [70-154]</td>
<td>3.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>11KA</td>
<td>96 [58-143]</td>
<td>31 [20-42]</td>
<td>3.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>DHEA</td>
<td>514 [168-971]</td>
<td>2702 [1419-3895]</td>
<td>0.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PregS</td>
<td>10600 [3400-25305]</td>
<td>3738 [2853-7769]</td>
<td>2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>17OHPregS</td>
<td>416 [290-1174]</td>
<td>481 [370-683]</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>DHEAS</td>
<td>18744 [7847-64308]</td>
<td>139784 [58409-186697]</td>
<td>0.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>AdiolS</td>
<td>2711 [1228-9723]</td>
<td>25576 [12095-35882]</td>
<td>0.1</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

C₁₉-Steroids in 21OHD

Androgenic Cells in 21OHD

Red: 3βHSD
Green: Cyt $b_5$

The Future Of CAH Therapy
A Little History On Cortisone

• 1948: Hench Treats RA With Cortisone
• Hench Wins 1950 Nobel Prize
• 1950: Wilkins Treats CAH With Cortisone
• Wilkins Does Not Win Nobel Prize
• But He Has a Society Named After Him
• And in CAH, Progress Stops Here
How Else To Treat CAH?

**Hypothalamus**

- CRH

**Pituitary**

- ACTH

**Adrenal**

- Cortisol
  - DHEAS, Androgens
  - Skin, Bone, Etc

**Glucocorticoids**

**CRFR1 Antagonist**

**Abiraterone Acetate**
Abiraterone 100 mg/d in 21OHD
Primary End Point: Androstenedione

Auchus et al 2014 JCEM 99:2763
NBI-77860: CRFR1 Antagonist

ACTH: Subject 1003

ACTH: All Subjects (N=8)

17-OHP: Subject 1003

17-OHP: All Subjects (N=8)

Turcu et al J Clin Endocrinol Metab, in press
Future Studies

• Novel Therapies in Children & Adults
  – Abi, NBI, ATR-101, Others

• Biomarkers: Diagnosis & Management
  – LC-MS/MS Profiling

• Biochemistry of Key Enzymes
  – Strategies to Inhibit Androgen Synthesis

• Cell Biology of CAH Steroidogenesis
  – Zonation, Enzyme & TF Expression

• Patient Care Strategies
  – Optimizing Long-Term Outcomes
Summary: Classic CAH

- SW/SV Distinction Not Useful In Adults
- Most Should Continue Fludrocortisone
- Dissociate Androgen Excess & Adrenal Replacement Therapies
- Attention to Adrenal and Rest Tumors
- Progesterone Key To Female Fertility
- Sperm Banking for Males
- Genotype NCAH Pre-pregnancy
- Individualize Treatment Goals
Do’s and Don’ts

**DO**
- Try Hydrocortisone
- Use Fludrocortisone
- Follow PRA, BP
- Assess Testes
- Prog For Pregnancy
- Mechanical Depilation
- Genotype Nonclassics
- Separate Adrenal Replacement & Androgen Excess Rx

**DON’T**
- Suppress 17OHP
- Use Inverse Rhythm
- Use Prednisone [(Methyl) Predinsolone Instead]
- Recommend ADX
- Try to Replace Adrenal Insufficiency with HS Dex
- Stop Treatment
- Diagnoses Nonclassic 3βHSD Deficiency
“Today is a new day”
—Chicken Little