An Approach to Adrenal Insufficiency in Patients with Adrenoleukodystrophy
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Disclosures

I have no financial disclosures
Outline

• Review of Normal Adrenal Pathology
• Adrenal Insufficiency Screening Guidelines
• Treatment of Adrenal Insufficiency
• Androgen Insufficiency & Testicular Dysfunction
Normal Adrenal Physiology
Mineralocorticoid (Aldosterone)

Glucocorticoid (Cortisol)

Androgens (DHEA, Androstenedione)

Zona Glomerulosa

Zona Fasciculata

Zona Reticularis

Modified from *Williams Textbook of Endocrinology, 12th Ed, 2011*
Physiologic Effects of Glucocorticoids

- Stimulates Gluconeogenesis
  - Antagonistic to Insulin
- Protein Breakdown & Inhibits Protein Synthesis
- Promotes Lipolysis
- Amino Acids & Glycerol are used as Gluconeogenic Substrates

- NET EFFECT: Increases Production & Conserves Glucose for use by Essential Tissues (Brain)
Cortisol & Blood Pressure

- Increases Blood Pressure in Stressful Conditions:
  - High Concentrations of Cortisol act as a Mineralocorticoid
    - Increased Sodium & Water Retention
  - High Concentrations of Cortisol Increases Angiotensinogen Synthesis by the Liver & Increases the Vascular Reactivity to Vasoconstrictors
  - Cortisol is also required for enzymatic activity for the conversion of Norepinephrine → Epinephrine
  - Cortisol decreases capillary permeability to prevent hypotension
    - Decreases production & activity of nitrous oxide
    - Decreases Kinin & Prostaglandin Systems
Cortisol Secretion

Circadian Rhythm:
- Cortisol is low at onset of sleep
- Cortisol starts to rise between 2 & 4 am
- Cortisol Peaks at ~8 am
- Diurnal rhythm start to develop at 6-12 mo of age

Cortisol Deficiency ➔ Elevation of ACTH

Modified from Williams Textbook of Endocrinology, 12th Ed, 2011
Mechanisms for Adrenal Insufficiency in ALD

- VLCFA accumulate in adrenocortical cells starting in the fetal period
  - Zona fasciculata → Cortisol Deficiency
  - Zona reticularis → Androgen Deficiency
  - Spares the zona glomerulosa but mineralocorticoid deficiency has been described
- Mineralocorticoid deficiency causes salt-wasting
Pathophysiology of Adrenal Disease

- Lipid Peroxidation $\rightarrow$ Oxidative Stress $\rightarrow$ Apoptosis of Adrenocortical cells

- *In vitro* VLCFA accumulation alters the viscosity of the adrenocortical cell $\rightarrow$ impairs binding of ACTH to receptor $\rightarrow$ Adrenocortical atrophy & ↑ACTH

- VLCFA may also lead to a relative shortage of precursor cholesterol for steroidogenesis
Primary Adrenal Insufficiency

Cortisol Deficiency → Elevation of ACTH
• Loss of Diurnal Variation in ACTH & Cortisol

Androgen Deficiency → Lack of Secondary Sex Characteristics (no pubic hair)

Modified from *Williams Textbook of Endocrinology, 12th Ed, 2011*
# Signs & Symptoms of Primary Adrenal Insufficiency

**Chronic**
- Fatigue, Anorexia, Weight Loss/Lack of Weight Gain
- Intermittent Abdominal Pain
- Hyperpigmentation
  - Areaolae, Genitalia, Scars, Moles, Palmer Creases, Axillae, Pigmentary Lines in Gums, Posterior Helix of the Ear

**Acute**
- Nausea, Vomiting, Abdominal Pain
- Dehydration
- Hypoglycemia
- Hypotension
- Altered Mental Status
- Signs/Symptoms of Infection or other stress
Natural History of Adrenal Insufficiency in ALD

• ~86% of boys with ALD will have adrenal insufficiency

• Earliest report in literature of asymptomatic adrenal insufficiency is 5 months
  – Personal communications 3-5 months with newborn screening

• <1% of female heterozygotes develop adrenal insufficiency
# Presentations in Males with \textit{ABCD1} Mutations

<table>
<thead>
<tr>
<th>Phenotype (Frequency)</th>
<th>Description</th>
<th>Age of Onset</th>
<th>Frequency of Adrenal Insufficiency (AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood Cerebral Adrenoleukodystrophy (ALD) (31-35%)</td>
<td>Devastating Progressive Neurocognitive Decompensation (rapid progression 6 mo-2 yr)</td>
<td>1\textsuperscript{st} decade</td>
<td>79%</td>
</tr>
<tr>
<td>Adolescent Cerebral ALD (4-7%)</td>
<td>Similar to childhood ALD but slower progression</td>
<td>2\textsuperscript{nd} decade</td>
<td>62%</td>
</tr>
<tr>
<td>Adult Cerebral ALD (2-3%)</td>
<td>Dementia, behavioral changes, focal deficits without preceding AMN</td>
<td>After 2\textsuperscript{nd} decade</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Adrenomyeloneuropathy (AMN) (40-60%)</td>
<td>Progressive spastic paraparesis, sensory ataxia, sphincter dysfunction, diffuse hair loss</td>
<td>3\textsuperscript{rd}-4\textsuperscript{th} decade</td>
<td>70%</td>
</tr>
<tr>
<td>Adrenal Insufficiency, only (~10%, ~50% in childhood)</td>
<td>Primary adrenal insufficiency (typically cortisol &amp; androgen insufficiency)</td>
<td>Typically 3-10 years</td>
<td>100%</td>
</tr>
<tr>
<td>Asymptomatic (&lt;5%)</td>
<td>No neurologic or adrenal symptoms</td>
<td>&lt;4 years</td>
<td>&gt;50% develop AI</td>
</tr>
</tbody>
</table>

Epidemiology

- Primary Adrenal Insufficiency Lifetime Risk
  - Males – 86%
  - Females – <1%

- Female Case Series of 71 heterozygotes – 9 year old with primary adrenal insufficiency (both mineralocorticoid & glucocorticoid deficiency reported)
ADRENAL INSUFFICIENCY IN ASYMPTOMATIC ADRENOLEUKODYSTROPHY PATIENTS IDENTIFIED BY VERY LONG-CHAIN FATTY ACID SCREENING

Prachi Dubey, MD, MPH, Gerald V. Raymond, MD, Ann B. Moser, BA, Sidharth Kharkar, MD, Lena Bezman, MD, MPH, and Hugo W. Moser, MD

Journal of Pediatrics, 2005, 528-532
Dubey, et al.

- 49 asymptomatic males identified with ALD after screening based on family history (4.5±3.5 years)
- Cosyntropin Stimulation Testing (250 mcg)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Cortisol</td>
<td></td>
<td>&lt; 6 mcg/dL</td>
</tr>
<tr>
<td>Baseline ACTH</td>
<td></td>
<td>&gt;500 pg/mL</td>
</tr>
<tr>
<td>Cortisol after Cosyntropin</td>
<td>Change of &gt;7 mcg/dL</td>
<td>Cortisol &gt;18 mcg/dL</td>
</tr>
</tbody>
</table>
### Stages of Adrenal Dysfunction

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Baseline Cortisol</th>
<th>Baseline ACTH</th>
<th>Cortisol Response to Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Adrenal Dysfunction</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Adrenal Insufficiency</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Adrenal Insufficiency</td>
<td>Normal</td>
<td>Elevated</td>
<td>Abnormal</td>
</tr>
<tr>
<td>3</td>
<td>Adrenal Insufficiency</td>
<td>Low</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>
Table 1. Distribution of baseline adrenal function in the entire cohort (n = 49)

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline abnormal</td>
<td>24</td>
<td>(49%)</td>
</tr>
<tr>
<td>Baseline borderline</td>
<td>15</td>
<td>(31%)</td>
</tr>
<tr>
<td>Baseline normal</td>
<td>10</td>
<td>(20%)</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>(100%)</td>
</tr>
<tr>
<td>Eligible for follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up/started on ART</td>
<td>11</td>
<td>(22%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Prospectively followed</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
Dubey, et al.

Normal mineralocorticoid levels were reported in all 18 patients tested.

At end of study, 42/49 (86%) had adrenal dysfunction.
Newborn Screening
Current NYS Guideline for Adrenal Insufficiency

“Newborn boys see an endocrinologist to have baseline serum ACTH and cortisol level...For asymptomatic boys in childhood, monitoring of adrenal involvement with an annual clinical evaluation is recommended along with serum ACTH and cortisol performed every six months.”

Concerns with NYS Guidelines

- Infants do not have established circadian rhythms → no predictable diurnal variation in ACTH and cortisol
- Normal reference ranges for ACTH and cortisol in infants are not well established
- When to start screening and frequency to screen is not clear
Cortisol & ACTH during Infancy

- Basal Cortisol levels are lower in infancy
- Cortisol Binding Globulin (CBG) is lower in neonates
- Cortisol & ACTH secretion is pulsatile and unpredictable during infancy
Approach to Positive ALD Newborn Screen

• Once ALD is confirmed by the metabolic consultant, referral to pediatric endocrinology
  – Goal is to be seen within a week

• Physical exam assess for signs & symptoms of adrenal insufficiency

• Counsel parents/caregivers to recognize signs & symptoms of adrenal insufficiency at home
“Baseline” Cortisol & ACTH vs. Cosyntropin (ACTH) Stimulation Test

Dealing with the lack of predictable diurnal variation in cortisol & ACTH:

• Algorithm allows for option to either draw “baseline” or do cosyntropin (ACTH) stimulation test as screen under the age of 2 years

• Personal Approach:
  – Give parents option under 1 year
  – At 1 year (assuming sleep patterns are normal), start with 8 am cortisol & ACTH
Frequency of Adrenal Insufficiency Screening

• New York State Guidelines suggest every 6 months

• Pediatric Endocrinology Proposed Guidelines:
  – Every 3-4 months under 2 years
  – Every 4-6 months after 2 years
Patient Presentation

- Baby boy identified on NYS Newborn Screen
- “Baseline” Labs were drawn at 2 weeks of age
  - Cortisol 1.3 mcg/dL
  - ACTH 29 pg/mL
Patient Presentation

• Baby boy identified on NYS Newborn Screen
• “Baseline” Labs were drawn at 2 weeks of age
  – Cortisol 1.3 mcg/dL ("low")
  – ACTH 29 pg/mL ("normal")
• 7 weeks of age – no hyperpigmentation, growing well
  – I recommended follow up testing in 3-4 months
• 4.5 months of age – hyperpigmentation noted in the axillary creases
Patient Presentation

- 4.5 months – High-dose (125 mcg) Cosyntropin stimulation test performed

<table>
<thead>
<tr>
<th></th>
<th>Time = 0</th>
<th>Time = 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (pg/mL)</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Cortisol (mcg/dL)</td>
<td>8.4</td>
<td>14.1 (normal ≥18 mcg/dL)</td>
</tr>
</tbody>
</table>

- Stress dosing of hydrocortisone was recommended
Patient Presentation

- Growing well at follow up. No notable progression of hyperpigmentation at 8.5 months. At 10.5 mo, mother noted worsening hyperpigmentation.

Repeat 8 am laboratory values:

<table>
<thead>
<tr>
<th></th>
<th>8 mo</th>
<th>9 mo</th>
<th>10.5 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (pg/mL)</td>
<td>348.6</td>
<td>244</td>
<td>387</td>
</tr>
<tr>
<td>Cortisol (mcg/dL)</td>
<td>10.6</td>
<td></td>
<td>7.8</td>
</tr>
</tbody>
</table>

- Certainly needs stress dosing of hydrocortisone
- Discussion about starting daily doses of hydrocortisone versus monitoring
Treatment
Treatment of Adrenal Insufficiency

• Standard treatment for primary adrenal insufficiency
  – Hydrocortisone supplementation (typically 3x/day)
  – Stress dosing with hydrocortisone – includes training for intramuscular injection of Solu-Cortef
  – 24 hour access to on-call endocrinologist to counsel regarding stress situations

• Monitor for mineralocorticoid deficiency
  – Guidelines will suggest drawing renin & electrolytes every 6-12 months once on daily hydrocortisone (treatment – salt & fludrocortisone daily)

• Androgen deficiency
Treatment in the Setting of Stress

• Definition of Stress?
  – Psychological Stress does *not* get covered

• For Fever (<101°F)/Mild Illness → Double Physiologic Hydrocortisone dose

• For Fever (≥101°F)/Moderate Illness → Triple Physiologic Hydrocortisone dose

• Surgery/Dental Procedures: need to know duration, pain, ability to take medication by mouth

• When unsure, error on the side of giving *more* hydrocortisone!
Treatment in the Setting of Stress

Injectable Hydrocortisone Training

https://www.youtube.com/watch?v=moSz5ZoTJFE
Safety
Long Term Follow Up

• Growth needs to be carefully monitored
  – Too Much Hydrocortisone  →  Impairs Linear Growth
  – Too Little Hydrocortisone  →  Symptoms of Adrenal Insufficiency (Poor Weight Gain  →  Impairs Linear Growth)

• Other signs of Iatrogenic Cushing Syndrome (Too Much Hydrocortisone)
  – Hypertension
  – Hyperglycemia/Diabetes
  – Loss of Muscle Mass
Caution with Other Medications

- Some medications can increase the clearance of hydrocortisone → increased dose requirement
  - Phenobarbital (anti-epilepsy)
  - Phenytoin (anti-epilepsy)
  - Rifampicin (antibiotic)
- Recommend repeat ACTH levels once on steady dose of medication
- Baseline dose of hydrocortisone may need to be 3+ times higher
- Error on the side of giving more hydrocortisone with stress
Androgen Deficiency & Testicular Dysfunction
Androgen Deficiency & Testicular Dysfunction

• Limited studies suggest ~¾ of adult men with ALD have biochemical testicular dysfunction

• Most report primary gonadal failure
  – VLCFA accumulate in the Leydig cells
  – VLCFA may interfere with androgen receptor
  – May have a degree of pituitary dysfunction → hypogonadotrophic hypogonadism
Concerns with Androgen Deficiency

- Decreased Bone Mineral Density → Increased Fracture Risk (Osteopenia/Osteoporosis)
- Mild Anemia
- Decreased Muscle Mass & Strength
- Increased Body Fat
- Decreased Energy & Endurance
- Dysthymia/Depression
- Reduced Libido & Spontaneous Erections
Androgen Deficiency & Testicular Dysfunction

Retrospective report of 26 men with ALD
• 46% - decreased libido
• 58% - erectile dysfunction
• Of 17 tested, 16 had symptoms of hypoandrogenism
  – 12% had frankly low testosterone
  – 88% had inadequate rise in testosterone in response to hCG

Androgen Deficiency & Testicular Dysfunction

Prospective, controlled study of 49 men with AMN

- 82% had testicular dysfunction
  - Elevated gonadotropins or low T:LH ratio
- 54% - erectile dysfunction
- Total testosterone levels did not differ from controls but free testosterone was lower in AMN patients

Androgen Deficiency & Testicular Dysfunction

- 3 month cross-over study of 15 males with ALD treated with DHEA 50 mg daily
- Restored DHEA-sulfate levels
- No change in VLCFA
- Associated with lower levels of some essential fatty acids
- No follow up studies
- Efficacy & safety unknown

Conclusions

• ALD Newborn Screening has the potential to identify those at high risk for life-threatening adrenal insufficiency and neurologic decompensation

• Guidelines are being revised to account for lack of predictable diurnal secretion of ACTH & cortisol during infancy

• We don’t yet understand the natural course of adrenal insufficiency and testicular dysfunction in ALD
Thoughts for Future Directions

• Collect data regarding the natural history of the endocrine dysfunction
  – Reassessment of current proposed guidelines will be necessary

• Consider looking for markers to predict adrenal dysfunction
THANK YOU!

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