No Conflicts or Disclosures

• I have no conflicts or disclosures

• I will not be discussing off-label use of any medications
Introduction

1. Discuss the diagnosis and management of congenital adrenal hyperplasia

2. Review treatment strategies for congenital adrenal hyperplasia

3. Discuss adult complications of congenital adrenal hyperplasia management
CAH

• AR condition resulting from enzymatic defects in adrenal steroidogenesis

• Impaired cortisol synthesis leads to chronic elevations of ACTH causing adrenocortical hyperplasia and oversecretion of precursors

• **Types**
  - 21 hydroxylase deficiency ~ 90-95%
  - 11β hydroxylase deficiency ~ 5%
  - 3β hydroxysteroid dehydrogenase deficiency < 1%
  - 17α hydroxylase deficiency <1%
  - Lipoid CAH (20,22-desmolase) < 1%
21 hydroxylase deficiency
21 hydroxylase deficiency

• Classic CAH:
  o Salt-wasting ~ 75%
  o Simple Virilizing ~ 25%

• Non-Classic CAH:
  o Late-onset
  o “Cryptic” CAH

Incidence:
• Classic CAH affects 1/5000 – 1/15,000 births
  o 1:300 in Alaskan Inuit populations

• Non-classic CAH affects 1/500-1/1000
  o 1:3 Ashkenazi jews are carriers; 1:27 are affected
  o 1:100 in NYC cohorts
# 21 Hydroxylase Deficiency

## Forms of 21-Hydroxylase Deficiency

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Classic Salt Wasting</th>
<th>Simple Virilizing</th>
<th>Nonclassic</th>
</tr>
</thead>
</table>
| Age at diagnosis   | Newborn to 6mo       | *Female*: Newborn to 2yr  
                      |                      | *Male*: 2-4yr        | Child to adult |
| Genitalia          | *Female*: Ambiguous  
                      | *Female*: Ambiguous | *Female*: Virilized  
                      | *Male*: Normal      | *Male*: Normal     |
| Incidence          | 1:20,000             | 1:60,000          | 1:1000     |
| Hormones           |                      |                   |            |
| Aldosterone        | Reduced              | Normal            | Normal     |
| Renin              | Increased            | Normal or increased | Normal     |
| Cortisol           | Reduced              | Reduced           | Normal     |
| 17-OHP             | >5000 ng/dL          | 2500-5000 ng/dL   | 500-2500 ng/dL (ACTH stimulation) |
| Testosterone       | Increased            | Increased         | Variable, increased |
| Growth             | −2 to −3 SD          | −1 to −2 SD       | Probably normal |
| 21-Hydroxylase activity (% of wild type) | 0                   | 1-5               | 20-50       |
“Cryptic” 21 hydroxylase deficiency

Laboratory data of parents with cryptic 21-hydroxylase deficiency.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Basal 17-OHP (nmol/l)</th>
<th>60 min 17-OHP (nmol/l)</th>
<th>Basal Cortisol (nmol/l)</th>
<th>60 min Cortisol (nmol/l)</th>
<th>ACTH (pmol/l)</th>
<th>Androstenedione (nmol/l)</th>
<th>Test. free (nmol/l)</th>
<th>Test. total (nmol/l)</th>
<th>DHEA (nmol/l)</th>
<th>DHEAS (nmol/l)</th>
<th>Plasma renin activity (μg/l per hour)</th>
<th>Epinephrine (pmol/l)</th>
<th>Metanephrine (pmol/l)</th>
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<tr>
<td>2</td>
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<td>125</td>
<td>395</td>
<td>497</td>
<td>5.3</td>
<td>6.0</td>
<td>10</td>
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<td>2290</td>
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<td>3.3</td>
<td>1.7</td>
<td>1.7</td>
<td></td>
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</table>

*To convert from SI units to metric: 17-OHP×33.1 ng/dl; cortisol×0.0362 g/dl; ACTH×4.54 pg/ml; androstenedione×28.65 ng/dl; free testosterone×0.288 pg/ml; testosterone×28.82 ng/dl; DHEA×28.82 ng/dl; DHEAS×36.9 g/dl; epinephrine×0.183 pg/ml; and metanephrine 0.192 pg/ml.

*bSub-normal cortisol level defined as 60-min stimulated cortisol=500 nmol/l (21, 22).

*Elevated for age and sex.

Basal 17 OHP levels 200-2,600 ng/dL
Fig. 5. Nomogram relating baseline to ACTH-stimulated serum concentrations of 17-OHP. The scales are logarithmic. A regression line for all data points is shown.
11-β hydroxylase deficiency
11-β hydroxylase deficiency

• Presents with virilization and low renin, low aldo HTN due to overproduction of DOC
  o Hypokalemia is variable

• Treatment involves glucocorticoids + mineralocorticoids

• Non-classic 11β-OHD CAH has been reported (rare)
  o Normotensive children with mild virilization or precocious pubarche
  o Adults with hyperandrogenism, woman with infertility
3β hydroxysteroid dehydrogenase deficiency
3β hydroxysteroid dehydrogenase deficiency

- Decreased production of mineralocorticoids, glucocorticoids, and sex steroids
  - Virilization of females
  - Undervirilization of males

- Treatment involves glucocorticoids and mineralocorticoids

- Non-classic 3β HSD deficiency exists (rare)
  - Hormonal criteria for diagnosis is controversial
  - Genotyping may be useful in milder cases
17α hydroxylase deficiency
17α hydroxylase deficiency

- Impaired cortisol and sex steroid synthesis

- Presents with HTN, hypokalemia, and metabolic alkalosis
  - Low renin, low aldo HTN

- Males are undervirilized

- Women fail to develop secondary sex characteristics (T1 breasts, T1 pubic hair)
  - Gonadotropins elevated
Congenital lipoid adrenal hyperplasia
Congenital lipoid adrenal hyperplasia

• Caused by mutations in the steroidogenic acute regulatory protein (StAR)

• Failure of transport of cholesterol from the outer to inner mitochondrial membrane (rate-limiting step)

• Deficiency of all adrenal and gonadal steroid hormones

• Fatal in infancy in 2/3 of cases
Diagnosis of CAH

• First morning 17 OHP (if suspecting 21 OHD)
  o 11-deoxycortisol (11 OHD)
  o DHEAS (3 β HSD)
  o DOC or Corticosterone (17 α OHD)
  o Adrenal imaging (Lipoid CAH)

• If borderline, an ACTH stimulation test with precursor product ratios
  o Esoterix reference book

• Genotyping is reserved for equivocal cases
Management of CAH
Management of Adult CAH

• **Goals of therapy:**

  1. Prevention of adrenal and gonadal hyperplasia
  2. Prevention of long-term consequences of adrenal replacement
  3. Preservation of fertility
Mineralocorticoid Treatment in CAH

- Fludrocortisone acetate at 0.05–0.2 mg/d

- Goal of suppressed or low-normal PRA
  - Blunts the hypovolemic drive to ACTH production

- Monitor plasma potassium, PRA, and BP
  - Goal of normokalemia, low PRA, avoidance of orthostasis

- Salt craving is uncommon
Glucocorticoid Treatment in CAH

Therapy Goals

• Suppression of adrenal androgen secretion without total suppression of the HPA axis

• No glucocorticoid therapy is able to simulate the normal cortisol circadian rhythm and there is no consensus on how to dose glucocorticoids
Diurnal 17 OHP Patterns in Treated Salt-wasting CAH

- N = 36 pts w/ classic CAH
- Median age, 12.3 yr (range 6.1–18.8)
- On HC bid (9A, 9P) or tid (8A, 3P, 10P) at 18 mg/m²/d
Glucocorticoid Treatment in CAH

Biochemical Monitoring

• Most authors recommend monitoring labwork at a standardized time before the administration of the morning glucocorticoid dose.

• Single measurements of 17OHP concentrations may be unreliable due to diurnal variability.
  o Early am androstenedione levels correlate well with the degree of adrenal suppression.
  o 24 hr urine ketosteroids reflect daily adrenal suppression.
  o Salivary 17 OHP and/or androstenedione have also been shown to correlate with adrenal suppression.

• Reasonable target 17 OHP levels ~ 400-1200 ng/dl but should be individualized.
Glucocorticoid Treatment in CAH

UK Audit of CAH Care

• Survey of 30 teaching centers

• Great variability in GC regimens
  o Hydrocortisone > Dexamethasone > Prednisolone
  o 60% administered a higher dose in the evening
  o 21% administered a single dose at bedtime only
  o 16% used weight based dosing
NIH Protocol for CAH Management

Adult CAH Patient

Classic

Female

- Long-acting GC$^{1,2}$ + fludrocortisone;
- Genetic counseling$^3$;
- GYN evaluation by experienced surgeon;
- DXA;
- Osteoporosis prevention;
- ± counseling for sexual issues;
- GC stress dosing

Male

- Long-acting GC$^1$ + fludrocortisone;
- Genetic counseling$^3$;
- Testicular ultrasound;
- ± DXA;
- GC stress dosing

Nonclassic

Female

- Treat according to symptoms: OC ± antiandrogen ± GC$^{1,2}$;
- Genetic counseling$^3$;
- GC stress dosing if receiving GC

Male

- No treatment necessary;
- ± Testicular ultrasound;
- Genetic counseling$^3$

- Dex 0.25-0.5 mg/d qHS for males and non-reproductive age females
- HC (2-3 doses) or prednisone (2 doses) in reproductive age females
Adrenalectomy for CAH

• Not recommended as routine

• Select cases:
  o Failed medical therapy
  o Patients with salt wasting CAH and infertility

• Advantages:
  o Reduces the risk of virilization in females
  o Allows for treatment with lower GC doses

• Disadvantages:
  o Surgical risk
  o Possible increased risk of adrenal crisis due to loss of protective residual adrenal function
  o Possible loss of hormones that may have beneficial effects (epi, DHEA)
  o Hyperpigmentation
• 18 pts, 3 as part of a research protocol and 15 with chronic non-compliance

• 2/18 were male (XY), 16/18 female (XX)

• Followed for 5 yrs

• Virilization improved in all patients, infertility improved

• Patient satisfaction high after adrenalectomy

• 5/18 had ≥ 1 adrenal crisis

• Hyperpigmentation was observed in > 50% patients if HC dose was reduced < 11 mg/m²
Complications of CAH Management
# Bone Health in Adults with CAH

## Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaaskelainen <em>et al.</em></td>
<td>32 (30 classic, 16 female, 16–52 yr)</td>
<td>Patient BMD Z-scores lower than Finnish population mean (lumbar spine, −0.52; <em>P</em> = 0.045; femoral neck, −0.83, <em>P</em> &lt; 0.001); long-term glucocorticoid dose negatively correlated with BMD Z-score; patients receiving longer-acting glucocorticoids had lower BMD than patients receiving hydrocortisone</td>
</tr>
<tr>
<td>King <em>et al.</em></td>
<td>26 classic females (21–71 yr)</td>
<td>Patients BMD Z-scores, T-scores, and lumbar spine measurements significantly lower than controls (unaffected sisters); osteopenia present in 45% salt-losers, 13% simple virilizers, 11% controls; patients with osteopenia had lowest levels of adrenal androgens</td>
</tr>
<tr>
<td>Sciannamblo <em>et al.</em></td>
<td>30 classic (12 female, 16–29 yr)</td>
<td>Whole-body BMD measurements significantly lower than controls (<em>P</em> &lt; 0.03); bone metabolism markers (serum bone-specific alkaline phosphatase and C-terminal telopeptide of type I collagen) higher in CAH patients than controls (<em>P</em> &lt; 0.04)</td>
</tr>
<tr>
<td>Bachelot <em>et al.</em></td>
<td>45 (35 classic, 36 females, 18–47 yr)</td>
<td>Osteopenia present in 52% of salt-losers, 42% of simple virilizers, and 20% of nonclassic patients at femoral neck and 39% of salt-losers, 33% of simple virilizers, and 30% of nonclassic patients at lumbar spine; osteoporosis found in 7%; negative correlation between BMD T-score and hydrocortisone dose</td>
</tr>
<tr>
<td>Falhammer <em>et al.</em></td>
<td>61 females (55 classic, 18–63 yr)</td>
<td>Osteopenia in 48% of patients &lt;30 yr old, 73% of patients ≥30 yr old, and 21% of age-matched controls; patients had lower BMD than controls at all measured sites (<em>P</em> &lt; 0.001); more osteoporotic fractures (vertebrae, wrist, and hip) in patients vs. controls (<em>P</em> = 0.058)</td>
</tr>
</tbody>
</table>
Final Adult Height in CAH

FIG. 3. Random-effects metaanalysis of corrected-height SDS. ◇, Overall estimate from the metaanalysis; ■, point estimate of the result of each study; the horizontal line that runs through the square and the width of the diamond represent the CI. SV, Simple virilizers; SW, salt wasters.
Testicular Adrenal Rest Tissue (TART)

- The prevalence of testicular adrenal rests in boys with classic CAH aged 2–18 yr varies from 21–28%
  - Limited studies in NCCAH males

- Benign, typically bilateral and often related to suboptimal therapy

- Usually decrease in size after optimization of GC therapy

- Typically near the mediastinum testes

- No malignant features
Expression of GATA Factors and Their FOG Cofactor Proteins during Gonadal and Adrenal Development

Contribution of cells from adrenogenital primordium and neural crest cells ultimately give rise to the cortex and medulla of the mature adrenal gland.

High Prevalence of Testicular Adrenal Rest Tumors, Impaired Spermatogenesis, and Leydig Cell Failure in Adolescent and Adult Males with Congenital Adrenal Hyperplasia

NIKE M. M. L. STIKKELBROECK, BARTO J. OTTEN, ARIFA PASIC, GERRIT J. JAGER, C. G. J. (FRED) SWEEP, KEES NOORDAM, AND AD R. M. M. HERMUS

Departments of Pediatric Endocrinology (M.M.L.S., B.J.O., C.N.), Endocrinology (A.P., A.R.M.M.H.), Radiology (G.J.J.), and Chemical Endocrinology (C.G.J.S.), University Medical Center Nijmegen, 6500 HB Nijmegen, The Netherlands

• 17 men with 21 hydroxylase deficient CAH, ages 16-40 y/o
  o 14 salt wasters, 3 simple virilizing CAH
  o 16/17 had TART
  o 11/17 had low testosterone levels
  o 3/11 were azospermic; 4/11 had oligospermia
Infertility and CAH - Men

- Men with classic CAH often develop oligospermia and infertility

- Adrenal rest tumors
  - Compression of the seminiferous tubules leads to irreversible damage and azoospermia
  - Paracrine effect on the surrounding tissue

- Eval: Total testosterone, Inhibin B (gonadotropins may be suppressed), semen analysis

- Treatment: Optimize GC therapy
  - Testis-sparing surgery
Can you get Ovarian Adrenal Rest Tumors (OART)?

- Yes!
- But less common
- Only 11 cases reported
- Difficult to distinguish from PCOS
Case Reports - OART

- Ovarian adrenal rest tissue in congenital adrenal hyperplasia--a patient report (Netherlands, J Pediatr Endocr Metabol 2006)

- Ovarian adrenal rest tumor in a congenital adrenal hyperplasia patient with adrenocorticotropic hormone hypersecretion following adrenalectomy (Israel, Horm Res Paediatr 2010)

- Ovarian adrenal rest tumour in a patient with chronically untreated congenital adrenal hyperplasia (Oklahoma, British Journal of Urology International 2011)
Infertility and CAH - Women

- Women with classic CAH have decreased fecundity
  - Hyperandrogenism, anovulation
  - Inadequate reconstructive surgery

- Fertility rates are proportional to the amount of enzymatic activity

- In women who do conceive, adrenal androgens should be followed every 2-3 wks

- HC or prednisone should be used to avoid suppression of the hypothalamic-pituitary-adrenal axis of the fetus
Should we screen for adrenal rest tumors in adolescents/adults with CAH?

  - All males with classic CAH should be periodically screened from adolescence for testicular adrenal rest tumors (2)
CAH and Adrenal Adenoma

- There is a high incidence of adrenal masses in patients with CAH
  - 82% in homozygous CAH
  - 45% in heterozygous patients

- Adrenal adenoma, hemangioma and myelolipoma

- Adrenal carcinoma has been rarely reported
Giant adrenal myelolipoma associated with 21-hydroxylase deficiency: unusual association mimicking an androgen-secreting adrenocortical carcinoma

- 57 y/o presented w/ 15 cm Lt adrenal mass, CT -30 HU
- Labs noted elevated androstenedione
- Suspected adrenocortical carcinoma, androgen secreting
- Histology confirmed myelolipoma
- Hyperandrogenism persisted post-op
- Pt confirmed to be a compound heterozygous carrier in CYP21A2 gene

*Figure 1. Axial CT image (A), axial MR T2-weighted image (B), and in-phase (C) and out-of-phase (D) T1-weighted images show a large heterogeneous left adrenal soft tissue mass (arrowheads; A, B and C) with substantial amount of interweaving free fat tissue (*; B). The free fat tissue is seen as low CT density (A) and low MR intensity (B and C) areas within the lesion. There is also a 1.5 cm nodule with similar features in the right gland (white arrow; A and D).*
Table 2. Reported cases of adrenal myelolipoma associated with congenital adrenal hyperplasia (CAH)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>CAH</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Adrenal presentation</th>
<th>Size (cm)</th>
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<tbody>
<tr>
<td>Schindler (19)</td>
<td>1975</td>
<td>21OH</td>
<td>53</td>
<td>F</td>
<td>ND</td>
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<td>Boudreaux and cols. (20)</td>
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<td>Barr and Giltman (21)</td>
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<td>400 g</td>
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<td>Iwamoto and cols. (25)</td>
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<td>32</td>
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<td>M</td>
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<td>Allison and cols. (30)</td>
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<td>Multi and bilateral</td>
<td>43, 8 and 24</td>
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<td>25 and 23</td>
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<td>Sakaki and cols. (35)</td>
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<td>Nigawara and cols. (36)</td>
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<td>Hagiwara and cols. (8)</td>
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<td>John and cols. (17)</td>
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<td>Present case</td>
<td>2009</td>
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<td>Bilateral</td>
<td>10 and 1.5</td>
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</tbody>
</table>
Prenatal Issues with CAH
Prenatal Diagnosis of CAH

- Measurements of amniotic fluid 17-OHP, HLA typing of fetal cells, and direct analysis of fetal CYP21A2 genes in amniocytes or CVS samples have all been used.

- **Analysis of CYP21A2 gene is now the method of choice**
Prenatal Treatment of CAH

• Considered experimental

• Treatment aims to reduce female genital virilization and the need for reconstructive surgery

• Rationale is that suppression of fetal pituitary ACTH secretion by exogenous glucocorticoid would prevent or reduce virilization of the external genitalia of affected females

• AR inheritance
  o If 1 child is affected, there is a 25% risk in future offspring
  o Potentially beneficial for only 1 in 8 fetuses

• Treatment is with dexamethasone
  o Not metabolized by placental 11 β2 HSD
  o Does not bind to maternal CBG
  o Must be initiated by 6 wks gestation, no later than 9 weeks
11\(\beta\) HSD1
Liver
Adipose
CNS

11\(\beta\) HSD2
Colon
Salivary gland
Placenta
Fig. 2. Timetable of female sexual differentiation. [Modified from P. Saenger et al.: Diagnosis in Andrology, vol 4 (edited by S. J. Kogan and E. S. E. Hafez), Martinus Nijhoff Publishers, Boston, 1980, pp 31–52.]
Prenatal Treatment of CAH

• **Potential Fetal Risks:**
  - Children exposed to DEX during the first trimester had an impaired verbal working memory
  - Low self-perceived scholastic competence
  - Increased self-rated social anxiety
  - Less masculine and more neutral behavior in short-term DEX-exposed boys (*Endocrine Care 2007*)

• **Potential Maternal Risks:**
  - Weight gain
  - Edema
  - Striae
Genetic Risk

- If both parents have classic CAH
  - → 2.5% risk of classic CAH
  - → 15% risk of non-classic CAH

- Sibling has CAH → 25% risk to siblings

- It is possible for a pt with NCAH to have a child with classic CAH?
  - Depends in part on the father’s carrier status and mother's genotype
  - Studies have shown that the risk is ~ 2.5%
Summary

• 21 hydroxylase deficiency is the most common form of CAH, with 75% presenting with salt wasting (classic CAH)

• Management involves mineralocorticoids and glucocorticoids with close monitoring for complications
  o Bone loss
  o Fertility impairment
  o TART

• Laboratory monitoring should be standardized in am before morning medication
  o Goal 17 OHP is 2-5 times ULN

• Prenatal treatment with dexamethasone is not indicated outside of clinical trials