

MANAGEMENT OF CAH IN ADULT PATIENTS

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Endorama

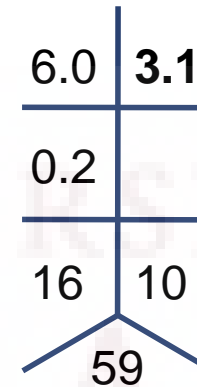
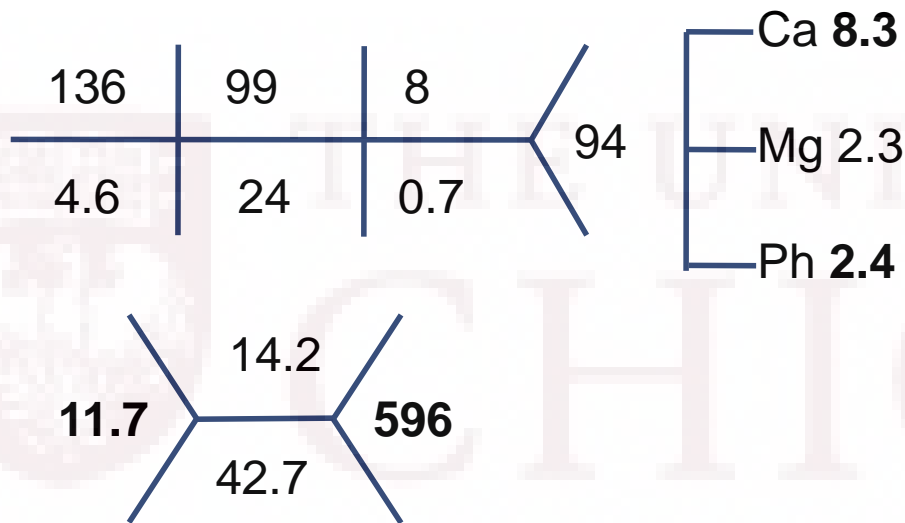
June 22, 2017

22 yo M with CAH presents with pruritis

- HPI:

- Several month history of progressive pruritis, worse in extremities (antecubital and popliteal fossae), also involving trunk now
- Previously presented to ED 2 weeks prior, prescribed prednisone but was unable to fill prescription and so represented to the ED with worsening pruritis/rash
- Reports Current flare is similar to prior flares, attributes to recent stress with school and trying to find a job

Admission Labs:



25-OH VitD: <7

ACTH 8.1 (6AM)

Consult questions: What additional evaluation for CAH is required, if any?
What treatment should be initiated/continued at this point?

Additional history:

- Hx of salt-wasting CAH, diagnosed at birth on neonatal screening
- Following intermittently with Pediatric Endocrinology –last seen 2 years ago
- Medications – stopped several months PTA due to feeling “overwhelmed” with taking too many medications, social stress
- Recent admission 3 months ago for eczema exacerbation, at that time he was reportedly taking:
 - prednisone 2.5 mg bid (hydrocortisone equivalent of 13.79 mg per meter squared)
 - fludrocortisone 0.1 mg bid
- Reports that he has been off of medications in the past for up to 4 months with no ill effects
- Previously using triamcinolone cream but reports ran out several months ago; denies recent OTC topical steroid use
- Per patient and primary service, no steroids given during this admission

ROS

Constitutional: No changes in weight, appetite, energy levels.

Vision: No photophobia, blurred vision, or other visual changes

ENT: No difficulty swallowing, sinus congestion, hearing deficits

CV: No palpitations, dizziness, chest pain, lower extremity edema.

Pulm: No dyspnea, wheezing, cough

GI: No abdominal pain, nausea, vomiting.

GU: No frequency, dysuria, hematuria, discharge, changes in libido.

ENDO: No heat or cold intolerance, glucose intolerance.

MSK: No myalgias, joint swelling, abnormal gait.

Neuro: No weakness, tremor, HA, numbness, paresthesias

Skin: **+very dry, pruritic skin.** No hyper/hypopigmentation.

Psych: No mood changes, anxiety, depression.

Past Medical History

PMH

- CAH
- Eczema
- Osteopenia
- Vitamin D deficiency

PSH

- ENT surgery
- Appendectomy

Social Hx

- Single, completed HS
- LAHW father
- Working in fast food restaurant

- No EtOH/drugs

Medications

- OTC hydrocortisone cream 1%
- Prednisone 2.5 mg bid (not taking)
- Fludrocortisone 0.5 mg bid (not taking)

Allergies: NKDA

Family Hx

- Eczema (brother)

Physical Exam

Vitals: BP 99/55 , **HR 115**, SpO2 98%, **Wt 44.5 kg (98 lbs)**, **Ht 157.5 cm (5'2")**, **BMI 17.9 kg/m²**

Gen: Young AA man, thin, no distress.

HEENT: No pharyngeal erythema. PERRL, EOMI. Minimal facial hair growth, acne+

Neck: Supple, thyroid not enlarged, no nodules

CV: Normal rate, regular rhythm, no murmurs, no LE edema

Pulm/Chest: Clear bilaterally, no rales, wheezes.

GI/Abd: Non-distended, soft, non-tender, no rebound, no guarding.

MSK: No proximal muscle weakness. Normal tone.

Neuro: AOx4, no focal deficits. Normal reflexes.

Skin: **Appears coarse, scaly patches on extremities and chest, sparing the face; areas of lichenification on arms and legs.**

Psych: Normal mood, affect, thought content.

Additional labs, studies:

ACTH 8.1 (6AM)

(Obtained at 2PM)

17-OHP - **pending**

Aldosterone - **pending**

Renin – **pending**

Repeat (9AM)

Cortisol 3.3

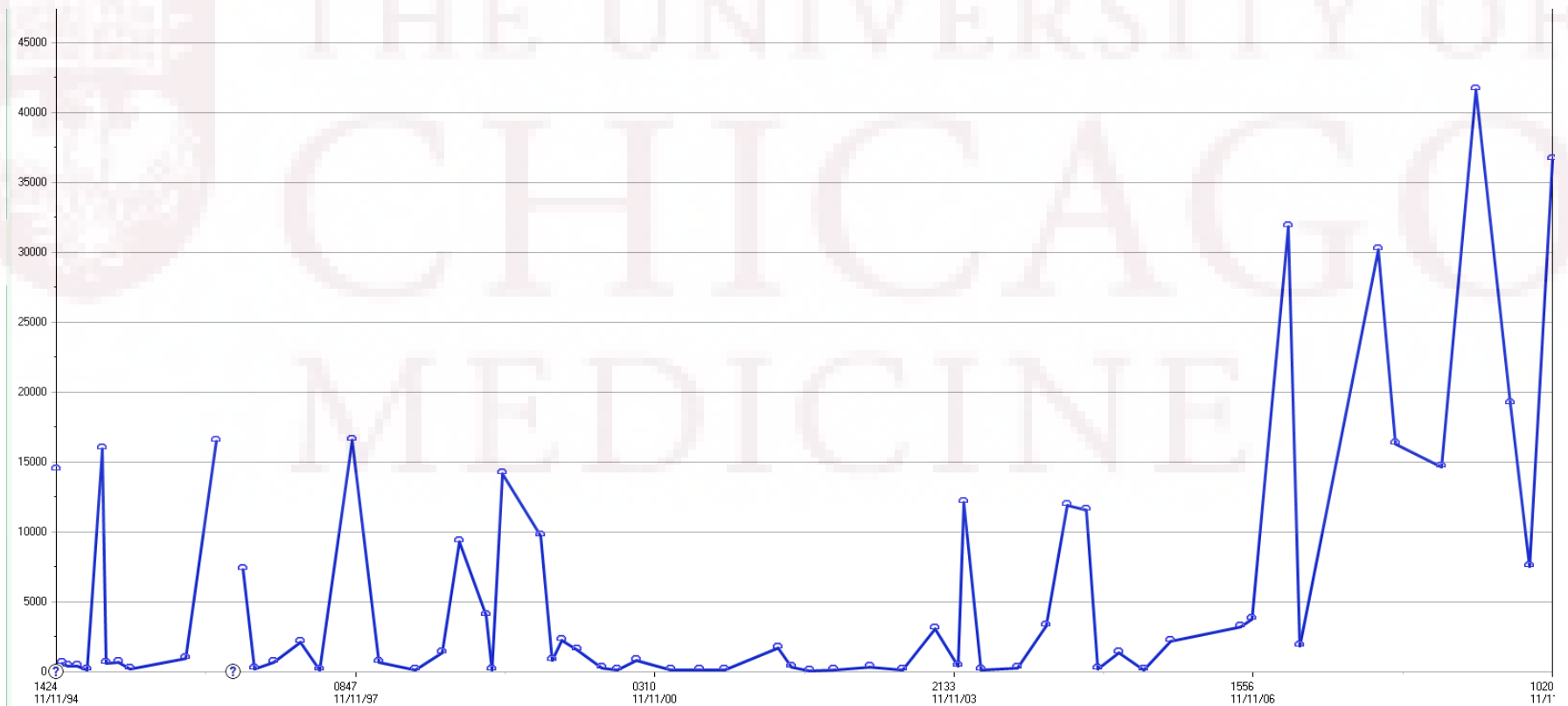
ACTH 97.2

A1c 5.8%

Remains tachycardic on exam; but orthostatic vitals are negative

Review of prior labs:

17-OHP 1994-2004



Review of prior labs:

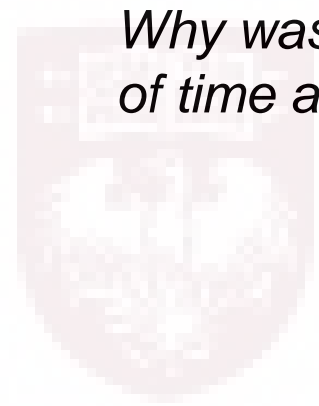
| | ACTH | 17-OHP | Aldosterone | Renin | Testosterone | Androstenedione |
|-----------------|-----------------------------|------------|-------------|---------|--------------|-----------------|
| Ref. Range | Latest Ref Range: <52 pg/mL | <220 ng/dL | <21 ng/dL | ng/mL/h | ng/dL | 65-210 ng/dL * |
| 1/19/2011 1643 | 53.7 ▲ | 11000 | | 14 | 307 | 1430 |
| 4/6/2011 1747 | 101.0 ▲ | 4550 | | 0.7 | 572 | 846 |
| 9/14/2011 1015 | 34.5 | 5640 | | 0.7 | | 791 |
| 12/14/2011 1020 | 686.0 ▲ | 36100 | | 13 | | 2640 |
| 4/11/2012 1038 | 1230.0 * ▲ | ND | | <0.6 | | ND |
| 8/17/2012 1018 | 146.0 ▲ | ND | | 1.6 | | ND |
| 7/17/2013 1648 | 97.6 ▲ | 3440 | | 3.1 | 401 | 65 |
| 5/14/2014 1018 | 370.0 ▲ | 20700 | | 4.5 | | ND |
| 10/8/2014 1650 | 165.0 * ▲ | 28900 | <4.0 | 1.4 | | ND |

* Based on Tanner V

Labs and Clinic notes reflect poor compliance with medication, multiple missed appointments

What is the clinical course of CAH in adulthood?

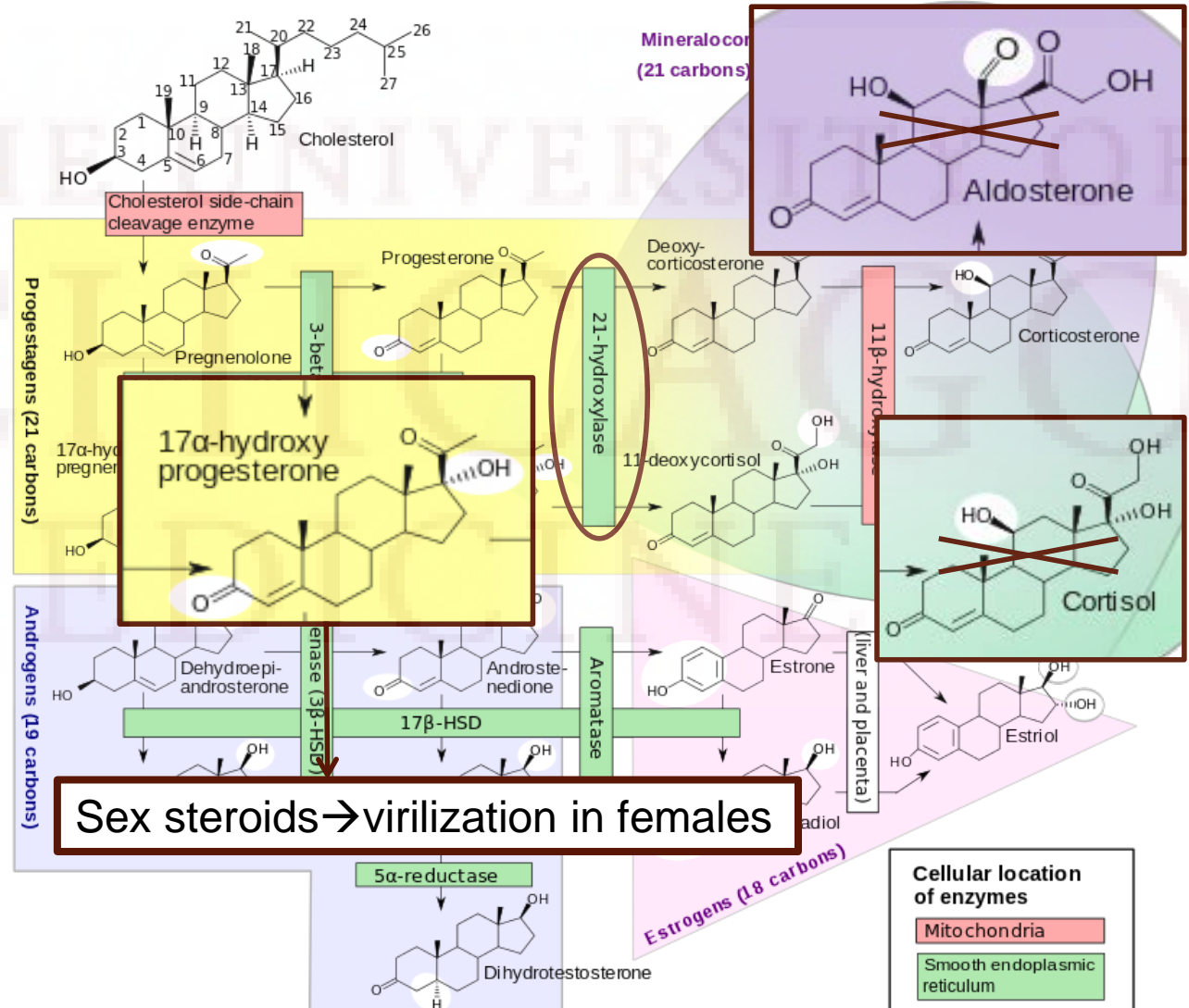
Why was he able to remain off of medications for extended periods of time and remain well?



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Steroidogenesis in CAH

- 21-hydroxylase deficiency accounts for 95% of CAH
- Classical CAH
 - 75% Salt-wasting (Aldosterone deficiency)
 - Simple virilizing
- Cortisol precursors accumulate and are diverted to sex hormone biosynthesis

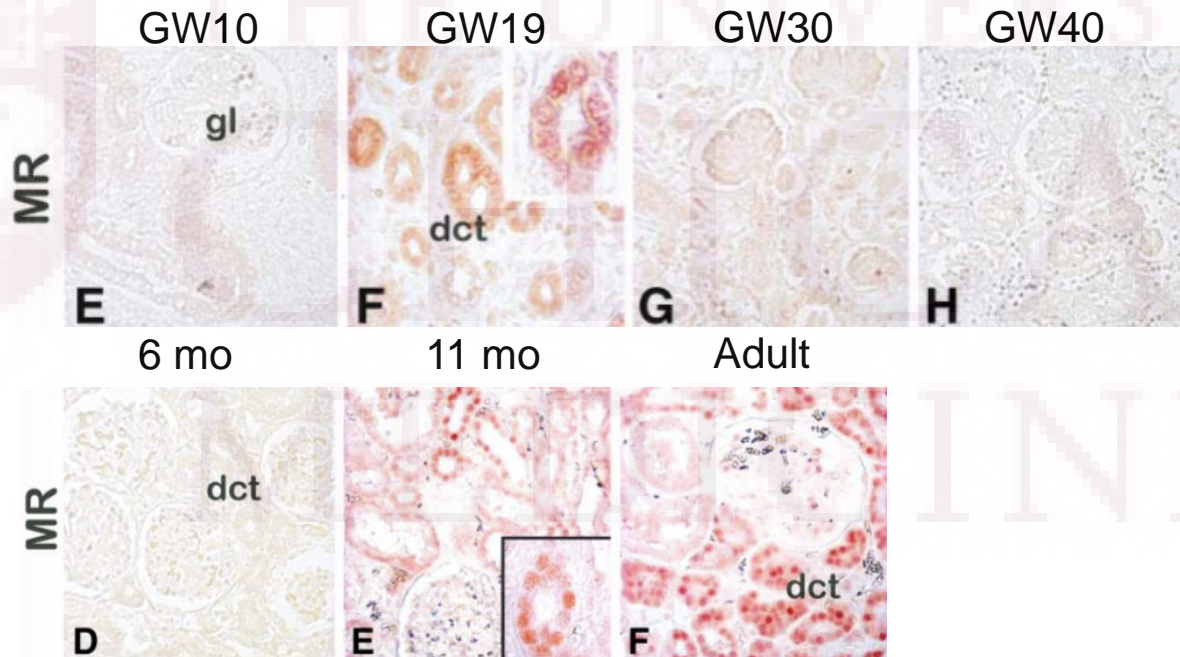


CAH – Variation in phenotype is common

- Diagnosis is by newborn screening of 17-OHP levels followed by genetic testing, confirmatory Cosyntropin Stimulation testing
 - 17-OHP is normally high in first 2 days of life
 - May be suppressed by prenatal steroid administration for lung maturation
- Disease severity correlates with *CYP21A2* (encodes 21 hydroxylase) allelic variation
 - >100 known mutations that preserve varying degrees of enzymatic function
 - 90% of CAH is associated with 10 mutations – screening feasible
 - Many patients are compound heterozygotes, leading to large degree of variability
 - For example, **Ile 172 Asn** preserves 2% of enzymatic function and leads to simple virilizing CAH

The neonatal kidney is not fully functional

- Neonatal kidney expresses low levels of **aldosterone receptor**



- Neonatal levels of **circulating aldosterone** are 6-10 times higher than in adults

What are the recommendations for steroid replacement?

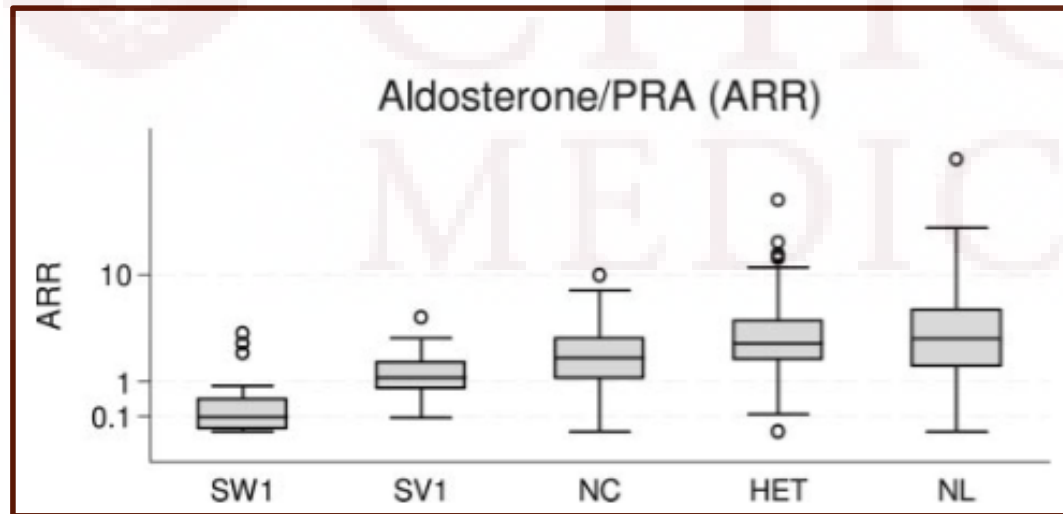
- Goals of therapy:
 - Replacement of steroid deficiency
 - Avoid effects of excess glucocorticoids
 - Adequate androgen suppression
- Forms of steroid replacement:
 - Hydrocortisone is preferred in childhood due to shorter half life
 - Prednisolone and dexamethasone not routinely recommended due to higher potency and potential for growth suppression
 - Adult height is inversely correlated with dose of GC during puberty
 - May switch to longer-acting GC after growth complete
- No formal recommendations in adults;
 - Survey of European pediatric endocrinologists:
 - 36% said they used HC (13.75 mg/m²)
 - 14% used prednisolone (4.75 mg/d) – avoid prednisone due to variability with hepatic conversion
 - 33% used dexamethasone (0.5 mg/d)
 - 17% not reported
- Mineralocorticoid replacement “has not been optimally studied”

TABLE 2. Maintenance therapy suggested in fully grown patients

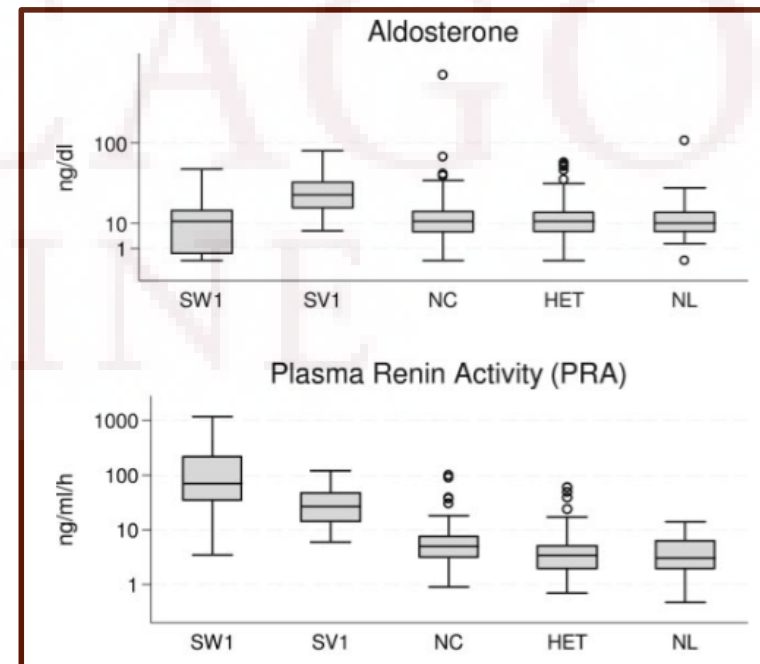
| Type of long-acting GC | Suggested dose (mg/d) | Daily doses |
|----------------------------|-----------------------|-------------|
| HC | 15–25 | 2–3 |
| Prednisone | 5–7.5 | 2 |
| Prednisolone ^a | 4–6 | 2 |
| Dexamethasone ^a | 0.25–0.5 | 1 |
| Fludrocortisone | 0.05–0.2 | 1 |

The Aldosterone-to-Renin Ratio (ARR) may be a helpful indicator in determining the degree of sodium wasting

- Objective: Determine whether serum aldosterone to plasma renin activity can be used as an index of sodium wasting in patients with 21-OHD CAH, heterozygotes, and normal individuals.
- N = 402
 - 244 Affected (Confirmed by genotyping)
 - 178 Unaffected (WT and Het)



SW = Salt wasting
SV = Simple virilizing
NC = Non-classical



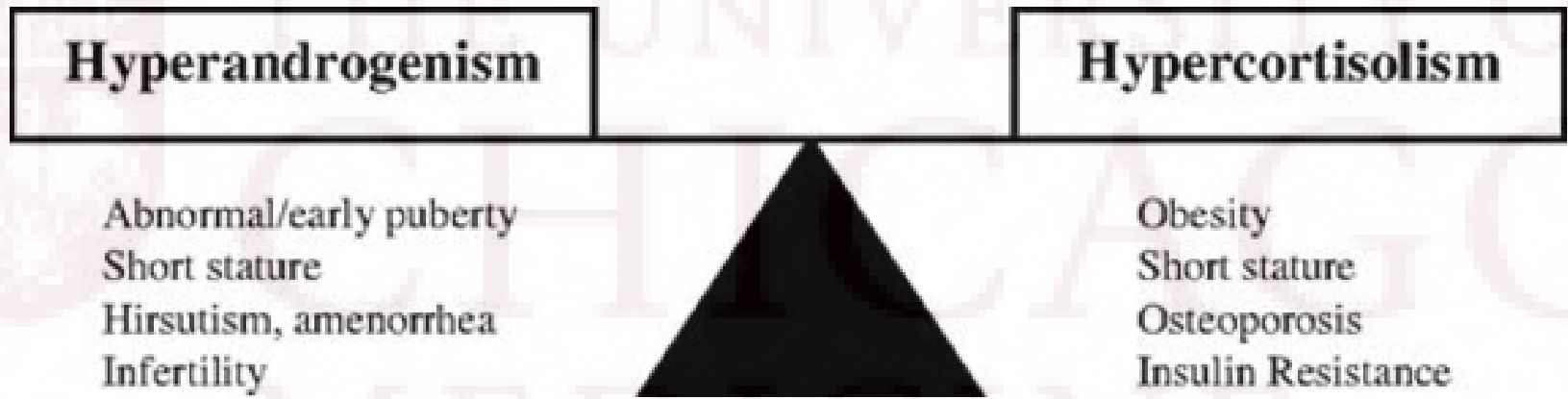
What additional screening, healthcare maintenance is required in adult patients with CAH?

- Mineralocorticoid sensitivity varies over time, and recovery from salt wasting has been reported
 - Kidney maturation
 - May also be due to extra-adrenal 21-hydroxylation (liver, skin, target tissues)
- Reassess need for continued mineralocorticoid replacement periodically based on:
 - Blood pressure
 - PRA (target upper normal – as low as possible while avoiding hypokalemia, orthostasis)
- Laboratory monitoring via consistently timed:
 - 17-OHP
 - AM androstenedione, gonadotropins and testosterone
 - Androstenedione/Testosterone >1 suggestive of Rest tumor
 - ACTH not generally useful
- BMD to assess for osteoporosis at peak bone mass (25 yo) and periodically
- Increase in **benign adrenal masses** in patients with CAH, thus routine screening is not indicated
- Increased HTN, BMI, possible increased risk of metabolic syndrome (no formal recommendation on screening)

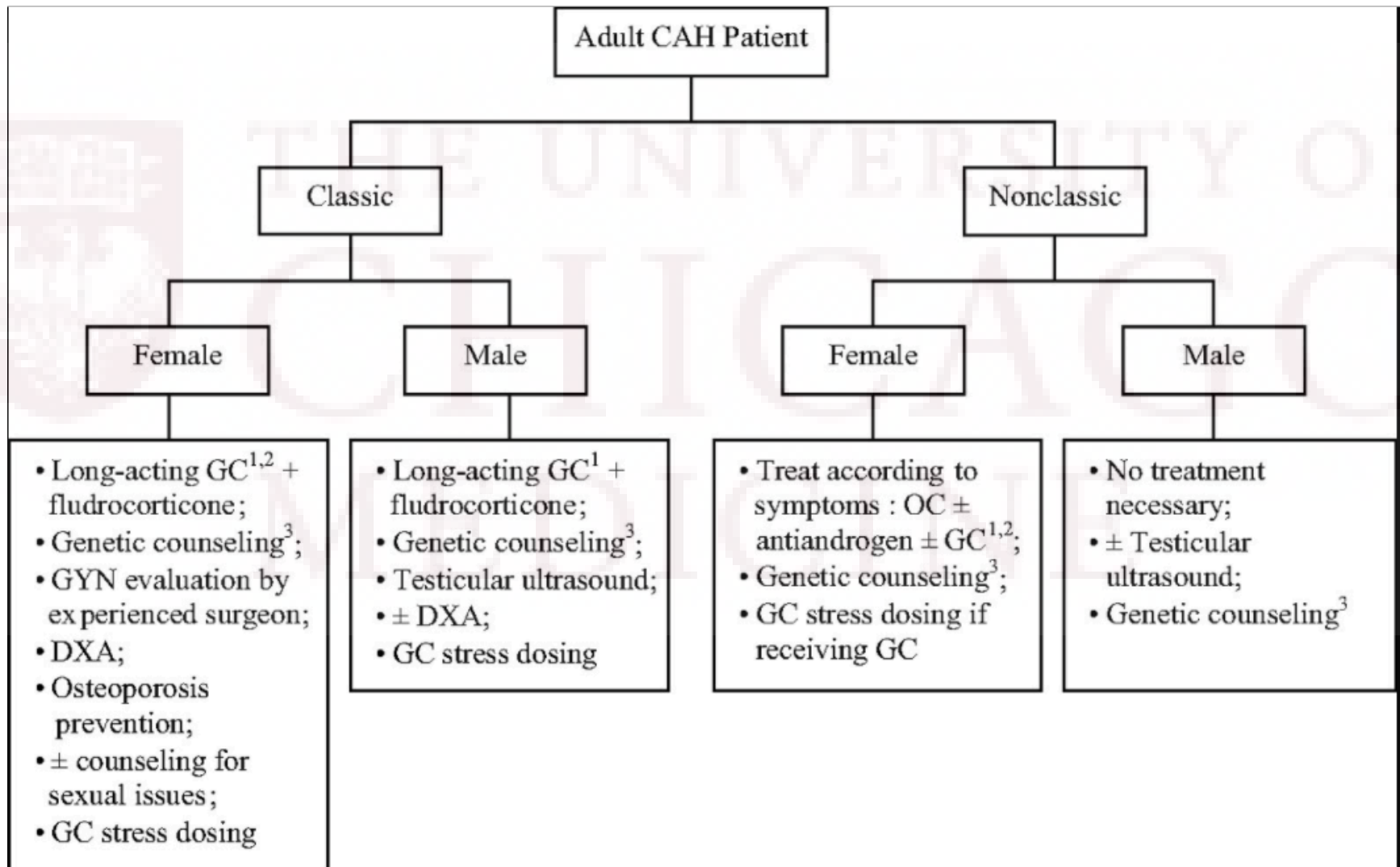
Gender-specific care in adult patients with CAH

- **Men:** Often asymptomatic unless ill or develop Testicular adrenal rest tumors (TARTs)
 - Testicular rest tumors
 - Occur in 21-28% of boys with CAH 2-18 years; up to 90% of adult men
 - ACTH-responsive. Associated with poor compliance, thought due to ectopic adrenal tissue in testes vs reprogrammed Leydig cells.
 - Usually benign but result in impaired fertility, pain
 - Elevated FSH associated with poor prognosis
 - Screen with exam/US annually in adults
 - Treated with intensification of glucocorticoid therapy
- **Women:** Hirsutism, menstrual irregularities
 - Treatment is similar to PCOS - may treat with OCPs to raise SHBG; however, avoid spironolactone as will antagonize effects of FC and predispose to dehydration
 - Pregnancy:
 - Avoid use of GC that cross the placenta (e.g. dexamethasone)
 - Stress-dose steroids indicated during delivery.
 - 20% increase in gestational diabetes in women with CAH
 - Adrenal Ovarian Rest Tumors – rarer than in males, not seen on conventional imaging
- **Genetic and Psychiatric Counseling**
 - Increased rates of depression, suicide attempts in patients with CAH

Overall Goals of CAH therapy



Overall Goals of CAH therapy



Clinical update

- Patient was discharged on prednisone 2.5 mg daily; fludrocortisone held pending Aldosterone/Renin
- Expedited follow up in adult endocrine clinic
- Started on Vitamin D3 5000 IU daily x 1 week followed by 2000 IU daily maintenance.
- Dietary counseling given elevated A1c
- Subsequent review of MAR reveals patient received 10 mg dexamethasone IV x1 in ED

Follow up visit in clinic:

- **Patient reports:**

- No lightheadedness, dizziness, malaise, fatigue.
- Initially with weight loss in setting of being ill, now regained weight.
- Recently started new job at Potbellies, taking a break from school and stress improved.
- Eczema is much improved, continues to take topical steroids to arms and legs.
- Reports compliant with prednisone 2.5 mg bid

- **Exam:**

- VS: BP 126/61, HR 71, Wt 47kg (103 lbs), Ht 157.5 cm (5'2"), **BMI 18.9 kg/m²**
- Skin improved

- **Prior labs returned:**

- 17-OHP 148 (RR: <220)
- Aldosterone <4.0 ng/dL (RR: <21)
- Renin **25** ng/mL/h
 - Na replete: mean 1.9, range ≤ 0.6-4.3
 - Na deplete: mean 10.8, range 2.9-24)
- ARR = Undet

Plan:

- Continue prednisone 2.5 mg bid – discussed transition to HC
- Resume fludrocortisone 0.1 mg daily

Repeat labs and studies ordered for 2 weeks following resumption of FC:

- BMP
- ACTH
- Cortisol
- 17-OHP
- Renin
- Aldosterone
- DHEA-S
- Testosterone

- DEXA
- Referral to Urology for testicular exam and US

Thank you

