OBJECTIVES

- To review the pathophysiology of adrenal crisis, adrenal hyperplasia, and thyroid storm
- To describe the clinical presentations of these conditions
- To present a schema to aid in proper and timely diagnosis of these entities
- To provide an update of the current treatment approaches for these conditions
ADRENAL INSUFFICIENCY

Pigmented face of primary adrenal insufficiency (illustration from Addison’s 1855 book: “On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules”)

CASE HISTORY AND PHYSICAL EXAM

- 2.5-yr-old male with 2 convulsions before age 2 yr, each associated with prolonged fasting and one with documented lab bG of 28 mg/dL
- 1-yr h/o hyperpigmentation
- PE: wt (5th %ile); ht (25th %ile); hyperpigmentation on lips, tongue, pressure points, and areas of skin trauma; fungiform papillae on tongue

LABORATORY DATA

- Fasting glucose = 10 mg/dL
- Sodium = 123 mEq/L
- Potassium = 6.8 mEq/L
- 8:00 AM cortisol = undetectable (5-24 µg/dL)
- 8:00 AM ACTH = >2000 pg/mL (20-100)
(ARS) QUESTION #1
In the case just presented, which of the following is the least likely etiology for the child’s adrenal insufficiency?

A. Autoimmune adrenalitis
B. Bilateral adrenal hemorrhage
C. Adrenoleukodystrophy
D. Mutation in AIRE gene
E. Hypopituitarism

1° ADRENAL INSUFFICIENCY: CUTANEOUS FINDINGS (I)

6 months 2 years

1° ADRENAL INSUFFICIENCY: CUTANEOUS FINDINGS (II)
ADRENAL INSUFFICIENCY: WHY ARE WE TALKING ABOUT THIS TODAY?

- Not as rare as you might think
- Symptoms non-specific
- Diagnosis frequently overlooked
- Untreated, outcome can be disastrous

MANIFESTATIONS OF CORTISOL DEFICIENCY

- **GI:** anorexia, nausea, vomiting, abdominal pain, and weight loss
- **Mental:** lethargy, apathy, confusion, and psychosis
- **Energy metabolism:** impaired gluconeogenesis, impaired fat mobilization and utilization, liver glycogen depletion, and fasting hypoglycemia
- **Cardiovascular/renal:** impaired free water excretion, impaired pressor responses to catecholamines, and hypotension
- **Pituitary:** unrestrained secretion of ACTH/MSH resulting in muco-cutaneous hyperpigmentation
- **Impaired tolerance to stress**
ManifEstatIons of AldosteronE DeFicienCy

- **Inability to conserve sodium**: decreased extracellular fluid volume, weight loss, hypovolemia, hypotension, decreased cardiac size and output, decreased renal blood flow, prerenal azotemia, increased renin production, weakness, postural syncope, and shock
- **Impaired renal secretion of potassium and hydrogen**: hyperkalemia, cardiac asystole, and mild acidosis

Adrenocortical Insufficiency: 1° Forms (I)

- **Congenital adrenal hyperplasia** (~60% associated with overt salt loss)
- **Autoimmune adrenalitis = Addison disease**: >70% of subjects have antibodies directed at adrenal and other endocrine glands, most commonly thyroid and β-cells; may occur as part of autoimmune polyendocrinopathy syndromes:
  - **Type I (Whitaker syndrome)** with mucocutaneous candidiasis and hypoparathyroidism (AIRE)
  - **Type II (Schmidt syndrome)** with hypothyroidism and T1DM

Adrenocortical Insufficiency: 1° Forms (II)

- **Infectious** (overwhelming bacterial sepsis, *e.g.*, meningococcemia, hemophilus influenzae = Waterhouse-Friderichsen syndrome; other, *e.g.*, Tb, cocci, histo, and blasto)
- **Congenital adrenal hypoplasia** (4 forms: sporadic (associated with hypopituitarism), autosomal recessive, X-linked associated with hypogonadotropic hypogonadism (caused by mutations in DAX-1 gene that codes for an orphan receptor of nuclear hormone receptor superfamily), and X-linked associated with muscular dystrophy and glycerol kinase deficiency)
ADRENOCORTICAL INSUFFICIENCY: 1° FORMS (III)

- Adrenal leukodystrophy and myeloneuropathy
- Congenital unresponsiveness to ACTH (in some cases associated with achalasia and alacrima)
- HIV infection (possibly related to direct infection, associated malignancy or infection, or to therapies)
- Other: adrenal hemorrhage, neoplastic infiltration, sarcoidosis, amyloidosis, hemachromatosis, bilateral adrenalectomy, medications (metyrapone, aminoglutethamide, ketoconazole, o,p'-DDD)

1° ADRENAL INSUFFICIENCY: CUTANEOUS FINDINGS (III)

1° ADRENAL INSUFFICIENCY: CUTANEOUS FINDINGS (IV)
1° ADRENAL INSUFFICIENCY: CUTANEOUS FINDINGS (V)

ADRENOCORTICAL INSUFFICIENCY: 2nd FORMS

- Exogenous or endogenous steroid withdrawal (common)
- Pituitary and hypothalamic lesions (rare)
- May be associated with hyponatremia, but not hyperkalemia or hyperpigmentation

ADRENOCORTICAL INSUFFICIENCY: DIAGNOSIS

- 1° adrenal insufficiency: low basal and, especially, stimulated (60') serum cortisol (and aldosterone) following IV bolus of 250 µg of synthetic ACTH 1-24 (Cortrosyn®); normal cortisol at any time ≥20 µg/dL
- 2° adrenal insufficiency: most commonly used stimulus is low-dose ACTH stimulation (0.5 µg/m² or 1 µg IV) following which cortisol should be ≥18 µg/dL; glucagon is an alternative stimulus
- Once diagnosis of 1° adrenal insufficiency is made in a male, test for adrenal leukodystrophy by measuring very-long-chain (C-26) fatty acids (VLCFA)
Acute Adrenocortical Insufficiency: Treatment

- **Volume expansion/hyponatremia**: saline
- **Hyperkalemia**: usually responds to high-dose glucocorticoid replacement, but may require specific emergency measures (e.g., calcium, insulin/glucose, bicarbonate, Kayexalate®)
- **Hypoglycemia**: IV dextrose
- **Cortisol and aldosterone deficiencies**: hydrocortisone hemi-succinate = Solucortef® @ 150 mg/m² (10X maintenance) by IV bolus followed by 150 mg/m²/d as a continuous infusion or in 4 divided doses (this provides significant mineralocorticoid effect as there is no pure parenteral mineralocorticoid on the market in U.S.; generic fludrocortisone is the orally available mineralocorticoid)

Chronic Adrenocortical Insufficiency: Treatment

- **Oral hydrocortisone** at ~10 mg/m²/d in divided doses (usually 1/2 in AM, 1/4 PM, and 1/4 hs to simulate normal diurnal variation); doses must be increased 2- to 3-fold during intercurrent illness and/or a parenteral form administered
- **Oral mineralocorticoid** (if indicated): fludrocortisone usually at 0.1 mg/d
- **Home parenteral glucocorticoid** (Solucortef® Act-o-vial)
- **Medic-Alert identification and emergency letter**

Question #2

A full-term infant is born with a fused scrotum, stretched phallic length of 2.5 cm, but bilaterally undescended gonads. The karyotype is 46,XX. While awaiting the result, what is the most important additional test to order?

A. LH  
B. FSH  
C. Estradiol  
D. 17-hydroxprogesterone (17OHP)  
E. Head MRI with contrast

Answer Now
ADRENAL HYPERPLASIA: IT'S MORE COMMON THAN YOU THINK!

TERMINOLOGY

- Classical adrenal hyperplasia = CAH (synonymous with congenital adrenal hyperplasia and more severe form)
  - Simple-virilizing = SV (~25%)
  - Salt-wasting = SW (~75%)
- Non-classical adrenal hyperplasia = NCAH (synonymous with late-onset and acquired adrenal hyperplasia and less severe form)

ADRENAL HYPERPLASIA SECONDARY TO 21-HYDROXYLASE DEFICIENCY

- Accounts for ~ 95% of cases of AH
- Classical form occurs in ~1:15,000-16,000 births in most populations (population most often affected in the world is Yupik Eskimos)
- Non-classical form occurs in ~1:1000 of the general Caucasian population, but occurs much more often in certain populations
ADRENAL HYPERPLASIA AMONG VARIOUS ETHNIC GROUPS

- 1:333 (0.3%) of Italians
- 1:53-63 (1-2%) of Hispanics and Yugoslavs
- 1:27 (3-4%) of Ashkenazi Jews of Eastern European origin

This makes NCAH possibly the most common human autosomal recessive genetic disorder.

21-HYDROXYLASE DEFICIENCY: CLASSICAL SALT-WASTING

Cholesterol
Pregnenolone → 17OH Pregnenolone → DHEA
Progesterone → 17OH Progesterone → Androstenedione
DOC → 11-desoxycorticisol → Testosterone
Aldosterone → Cortisol

21-HYDROXYLASE DEFICIENCY: CLASSICAL SIMPLE-VIRILIZING

Cholesterol
Pregnenolone → 17OH Pregnenolone → DHEA
Progesterone → 17OH Progesterone → Androstenedione
DOC → 11-desoxycorticisol → Testosterone
Aldosterone → Cortisol
21-HYDROXYLASE DEFICIENCY: NON-CLASSICAL

Cholesterol
Pregnenolone -> 17OH Pregnenolone -> DHEA
Progesterone -> 17OH Progesterone -> Androstenedione
DOC 11-desoxycortisol Testosterone
Aldosterone Cortisol

SERUM OR PLASMA LEVELS OF EPINEPHRINE, NOREPI NEPHRINE, GLUCOSE, INSULIN, CORTISOL, AND ACTH IN PATIENTS WITH CAH (●) AND HEALTHY MATCHED CONTROLS (○)

FACT: Proper glucocorticoid secretion by adrenal cortex is necessary for adrenomedullary organogenesis and epinephrine synthesis without which patients with CAH have additional risk factor for collapse during stress.

GLUCOCORTICOIDS: ROLE IN CATECHOLAMINE SYNTHESIS AND ACTION

Wong DL. Cell Mol Neurobiol 2006;26:891-900
VARIABLE PRESENTATIONS OF
ADRENAL HYPERPLASIA: FEMALES

- **Birth:** virilized genitalia (fusion of labio-scrotal folds and clitoromegaly) with or without salt loss (latter occurring typically between 7-10 d) (CAH)
- **Childhood:** early development of pubic hair with or without signs of virilization, including rapid linear growth (no salt loss) (NCAH)
- **Adolescence and adulthood:** hirsutism (60%), absence or loss of menstrual periods (54%), and acne (33%) (no salt loss) (NCAH)
- **Any age:** no symptoms (NCAH)

PRADER VIRILIZATION SCORES

FEMALES WITH CAH AND CLITOROMEGALY

Prader 3  Prader 5
VARIABLE PRESENTATIONS OF ADRENAL HYPERPLASIA: MALES

- Birth: not easily diagnosed (CAH or NCAH); already have high levels of testicular testosterone
- Infancy: signs of salt-loss (~75%) at 10-20 d of life (CAH)
- Childhood: premature pubarche without or with signs of virilization, including rapid linear growth and advanced bone age (no salt loss) (CAH or NCAH)
- Adolescence: not a common time of presentation (NCAH)
- Any age: no symptoms (NCAH)

PATHWAY FOR CAH SCREENING IN CALIFORNIA: TWO-TIER APPROACH

1st tier:
- filter paper
- Cholesterol measured in AutoDelfia Assay
- 4 birth-weight categories
- Preg 17OHP measured
- Preg 17OHPreg DHEA
- 2nd tier:
- filter paper
- (17OHP+AD)/cortisol measured by tandem MS (no birth-weight stratification)
- *from original specimen

LIMITATIONS OF SCREENING
- Sick term newborn (17OHP may reach 3300 ng/dL)
- Prematurity/birth weight (delayed expression of 11-OHase)
- Early sampling age
- Poor kidney function
- Stress
- Cross-reactivity of antibodies used in RIAs with other steroids

DIAGNOSTIC TESTS FOR CAH

- Blood
  - 17α-hydroxyprogesterone (17OHP) (stat) pre and post 250 µg of synthetic ACTH-1-24 (Cortrosyn® = Cosyntropin®)
  - karyotype/FISH for SRY to aid in sex determination
  - testosterone
  - electrolytes
  - renin
  - occasionally other cortisol precursors (e.g., specific compound S = 11-desoxycortisol)
  - + gene testing

- Radiology
  - pelvic ultrasound
  - genogram
  - + pelvic MRI (females)
**STANDARD MEDICAL TREATMENT OF CAH**

- **Oral hydrocortisone (ALL)**
  - At 12-18 mg/m²/d (or other glucocorticoid equivalent in teenagers and adults) in divided doses (usually 1/4 in AM, 1/4 in afternoon, and 1/2 at bedtime), with more at night to suppress physiological overnight rise in ACTH
  - Higher doses required at diagnosis
  - Doses must be increased 2- to 3-fold during intercurrent illness and or a parenteral formulation given
- **Oral mineralocorticoid (SALT-WASTERS):** fludrocortisone usually at 0.1 mg/d and possibly for simple virilizers with high renin levels
- **Sodium chloride (SALT-WASTERS):** 4 mEq/kg/day in divided doses for 1st yr
- **Home injectable glucocorticoid (ALL):** Solucortef® Act-o-vial
- **Medic-Alert identification (ALL)**
THYROID STORM

FAILURE TO REGULATE THYROID HORMONE LEVELS

GENERAL PRINCIPLES

- A life-threatening hypermetabolic state due to hyperthyroidism
- Mortality rate high (10-75%) despite treatment
- Frequency of thyroid storm in children is unknown, but increases with age
- Usually occurs as a result of previously unrecognized or poorly treated hyperthyroidism
- Thyroid hormone levels not helpful in differentiating between uncomplicated hyperthyroidism vs thyroid storm

PRECIPITANTS

- Severe infection
- Trauma
- DKA
- MI
- CVA
- PE
- Surgery
- Withdrawal of thyroid medication
- Iodine administration
- Excessive palpation of thyroid gland
- Ingestion of thyroid hormone
- Unknown etiology (20-25%)
**THYROID STORM: CLINICAL FEATURES**

- **Most common signs** are fever, tachycardia out of proportion to the fever, altered mental status, and diaphoresis
- **Clues** include a history of hyperthyroidism, exophthalmos, widened pulse pressure, and a palpable goiter
- Patients may present with signs of congestive heart failure
- Common GI symptoms include diarrhea and hyperdefecation

**THYROID STORM: THEORIES OF PATHOGENESIS**

- FT4 increased, but total T4 similar
- Increased target cell $\beta$-adrenergic receptor density
- Post-receptor modifications in signaling pathways

**THYROID STORM: PHYSICAL FINDINGS**

- **Fever**
  - Temperature consistently > 38.5°C
  - Patients may progress to hyperpyrexia
  - Temperature frequently > 41°C
- **Excessive sweating**
- **Cardiovascular signs**
  - Hypertension with wide pulse pressure
  - Hypotension in later stages with shock
  - Tachycardia disproportionate to fever
  - Signs of high-output heart failure
  - Cardiac arrhythmia [supraventricular arrhythmias are more common, (e.g., atrial flutter and fibrillation), but ventricular tachycardia may also occur]
THYROID STORM: PHYSICAL FINDINGS (II)

- Neurologic signs
  - Agitation and confusion
  - Hyper-reflexia and transient pyramidal signs
  - Tremors and seizures
  - Coma
- Signs of thyrotoxicosis
  - Orbital signs
  - Goiter

THYROID STORM: DIAGNOSIS

- Thyroid storm is a clinical diagnosis based upon suspicion and treated empirically
- Increased FT4 and FT3, decreased TSH
- Biochemical abnormalities are non-specific and may include leukocytosis, hyperglycemia, hypercalcemia, elevated transaminases, and hyperbilirubinemia
- Increased cortisol (normal level indicates adrenal insufficiency)

THYROID STORM: TREATMENT PRINCIPLES

- Initial stabilization includes airway protection, oxygenation, fluids, and cardiac monitoring
- Treatment can then be divided into 5 areas:
  - General supportive care
  - Inhibition of thyroid hormone synthesis
  - Blockade of peripheral thyroid hormone effects
  - Diminution of thyroid hormone release
  - Identification and treatment of precipitating events
TREATMENTS DIRECTED AT MAINTAINING HOMEOSTASIS

- Admit to ICU
- Hyperthermia: acetaminophen and cooling blankets (avoid ASA)
- Fluid and electrolyte testing/replacement
- Glucose
- Vasopressors
- Digoxin and diuretics as appropriate

TREATMENTS DIRECTED AT THYROID HORMONE SYNTHESIS AND SECRETION

- Inhibition of de novo thyroid hormone synthesis with thionamide drugs such as PTU or methimazole
- Inhibition of existing thyroid hormone release with iodine, iodide (Lugol solution), or lithium carbonate

WHAT IS LUGOL SOLUTION?

- Also known as Lugol iodine, this oral solution is specifically indicated for patients with thyroid storm or pre-operatively for a patient with hyperthyroidism
- It is a mixture of iodine, potassium iodide, and distilled water
- Remember you must not administer iodine until synthetic pathway has been blocked
- It is also used to enhance color and growth for coral in home aquaria!
TREATMENTS DIRECTED AT PREVENTING PERIPHERAL THYROID HORMONE EFFECTS

- Corticosteroids
- $\beta$-blockers (propranolol or esmolol)
- Guanethidine
- Reserpine
- Plasmapheresis

TREATMENT SUMMARY

Overall goal: Reduce circulating thyroid hormone levels and control symptoms:
- $\beta$-blockers: decrease adrenergic hyperactivity (sympathetic outflow)
- PTU: prevents synthesis of the thyroid hormone and peripheral conversion of T4 to T3
- Glucocorticoids: inhibit thyroid hormone production and decrease peripheral conversion of T4 to T3
- Sodium iodide (Lugol solution): high concentrations of iodide will initially suppress release of thyroid hormone
- General: treat cardiac symptoms, fever, and hypertension