THE ENDOCRINE SYSTEM - OVERVIEW

I. Overview of Posterior Pituitary, Thyroid, Genitalia, Adrenal, Pancreas, Parathyroid/Vitamin D, Growth Hormone, Puberty

II. Terminology
   A. Hypo vs. Hyper vs. Eu-
   B. Pseudo = “looks like” but isn’t.
      1. usually a receptor defect that mimics the absence of the ligand-hormone
      2. Causes unusually high levels of the hormone in question
   C. Primary vs. Secondary vs. Tertiary
      1. Primary – at the end-gland (e.g. thyroid, adrenal gland)
      2. Secondary – at the level of the Pituitary
      3. Tertiary – at the level of the hypothalamus

III. The “feedback system” of stimulatory and inhibitory regulation
   A. Hypothalamus-Pituitary-End Organ (see IV below)
   B. Non-Pituitary Hormones
      1. Insulin, glucagon, epinephrine
      2. Aldosterone
      3. Many others

IV. The hypothalamic-pituitary-end organ system of the anterior pituitary
   A. Thyroid - TRH-TSH-T4
   B. Adrenal - CRH-ACTH-Cortisol
   C. Sex steroids - GnRH-LH/FSH-Testosterone or Estradiol
   D. Bone Growth - GHRH-GH-IGF-1
   E. Lactation - Dopamine NEG Prolactin

THE POSTERIOR PITUITARY
   A. Arginine Vasopressin (AVP) = Anti-Diuretic Hormone (ADH)
   B. Normal Response
      \[ \begin{array}{|c|c|c|c|}
      \hline
      \text{↑Osmolality} & \text{↑ ADH} & \text{↓ Urine output} & \text{↑ body water} \\
      \text{↓ Osmolality} & \text{↓ ADH} & \text{↑ Urine output} & \text{↓ body water} \\
      \hline
      \end{array} \]
      Nl osmolality & Na

   C. Pathologic Response
      \[
      \begin{array}{|c|c|c|c|}
      \hline
      \text{Pathology} & \text{Pituitary} & \text{Kidney} & \text{Result} \\
      \hline
      \text{Diabetes Insipidus} & \text{NO ADH} & \text{↑ Urine output} & \text{↓ Body Water} \\
      \text{SIADH} & \text{↑ ADH} & \text{↓ Urine Output} & \text{↑ Body Water} \\
      \hline
      \end{array}
      \]
      ↑ Osmolality & Na
D. Causes of Central DI
   1. Congenital – Genetic or Absent Pituitary
   2. Acquired
      a. Pituitary or hypothalamic tumor - Craniopharyngioma
      b. Infiltrative process of pituitary stalk – Histiocytosis
      c. Trauma/Transsection/Surgery

E. Causes of SIADH
   1. CNS tumor/trauma
   2. Meds- Anticancer, antipsychotics, AEDs
   3. Pulmonary Process – Tumor or Infection

F. FIRST TEST(S) - URINE OSMOLALITY, Serum Osmolality, Serum Sodium, Urine Sodium

G. DI: Carefully Hydrate and give DDAVP, oral/Nasal/SQ

H. SIADH: Fluid Restrict to 1000 cc/m2/day

THYROID

I. Overview – Hypothyroidism, Hyperthyroidism, Euthyroid Problems
II. Hypothyroidism – Primary – pathology at end organ – Low T4, High TSH – Congenital vs Acquired
A. Congenital Hypothyroidism
   1. 1:3000 live births
   2. Identified on Newborn Screen with TSH level of >25 at >24 hours of age. Requires confirmation
   3. Untreated – many effects
      a. Prolonged jaundice
      b. Growth and developmental failure (neuron development)
      c. Constipation
      d. Coarse (puffy) facial features
      e. Umbilical hernia
      f. Ant Fontanelle slow to close

B. Acquired Hypothyroidism
   1. Most commonly secondary to autoimmune (Hashimoto)
      a. Defined by + antibodies
         • Anti Thyroid peroxidase (anti TPO) AND/OR
         • Anti Thyroglobulin (anti TG)
      b. Hashi’s often with only goiter (enlarged thyroid)
      c. + family history in 1/3
      d. Female>Male
      e. Part of Autoimmune Polyglandular Syndrome
         • DM-1, Addison’s, Hashimoto
2. Findings in Hypothyroidism
   a. Growth Failure (most common Endo cause of poor Growth)
   b. Mild weight gain, Dry Skin, Delayed relaxation phase of DTR’s, coarse hair.
   c. Lab
      - TSH – Elevated in Primary Hypothyroidism
      - Low T4, Free T4, +/- T3
      - Mild anemia – normocytic or microcytic
      - Positive Thyroid Ab’s (see above)

III. Hypothyroidism-secondary or tertiary
   A. Abnormality at pituitary or hypothalamus
   B. Usually associated with other Pit hormone deficiencies
      1. Post Cranial irradiation
      2. Post tumor of sella turcica
      3. Congenital absence of pituitary (e.g. SOD)

IV. Treatment for all Forms of Hypothyroidism
   A. Levothyroxine
      1. Newborn 10-15 mcg/kg/day
      2. Older 100 mcg/m2/day
      3. Start slow if longstanding or profound.
      4. Goal is to normalize TSH and T4 or FT4

V. Hyperthyroidism
   A. Overview
      1. Graves vs. Thyroiditis vs. Use of levothyroxine
      2. Labs show uppressed TSH and elev. T4, T3
   B. Children and Adolescents
      1. signs/sx
         a. Jittery, weight loss, agitation
         b. fatigue, heat intolerance,
         c. proptosis/exophthalmos
      2. Causes
         a. Graves – Most common Form –
            • Autoimmune Stimulation of TSH Receptor
         b. Thyroiditis – Release of pre-made thyroid hormone after damage
            • Hashimoto – Autoimmune
            • De Quervain – Painful – Viral?
         c. Surreptitious Use
3. Labs
   a. **TSH** - Suppressed to < 0.1 mIU/ml
   b. High T4 (except T3 toxicosis), High T3
   c. + TSH receptor Ab (TRAb), TSI - GRAVES
   d. + Anti TPO and +Anti TG – Hashi AND Graves

4. Treatment
   a. **Methimazole** (PTU with Hepatic Side FX)
      • Agranulocytosis is serious side effect
   b. Radioactive Iodine Ablation
   c. Surgical Thyroid Resection
   d. Short term symptomatic – Iodine, Prednisone, Propranolol

C. Neonatal Graves
   1. Occurs in 1 in 70 Pregnancies to mother with any history of Graves
   2. Intrauterine Findings
      a. Tachycardia/Heart Failure
      b. Poor Fetal Weight Gain
      c. Microcephaly
      d. Goiter
   3. Treatment
      a. Prenatally – maternal PTU
      b. Post Delivery PTU/Propranolol
   4. Self Resolves by 4 months in most cases

VI. Thyroid Nodules
   A. **Solitary nodules require aggressive workup in children**
      1. Ultrasound of Thyroid and Neck Lymph Nodes
      2. Uptake Scan
      3. Fine Needle Aspiration (FNA)
   B. Up to 20% are not benign
   C. Cysts and + ab’s usually indicate benign causes of nodules
   D. Worry if rapid growth, firm nodule, + FH of medullary thyroid CA, or history of neck irradiation
GENITALIA

I. Normal Development
   A. Male and Female undifferentiated until 9 weeks
   B. Y chromosome holds SRY gene, which causes gonads to develop into testicles:
      1. Testicles produce Testosterone and Dihydrotestosterone => virilization of external genitalia
      2. Testosterone stabilizes internal male “Wolffian” structures
      3. Anti-Mullerian Hormone from Testes causes the regression of the uterus, fallopian tubes and internal 1/3 of the vagina
   C. by 14 weeks, the genitalia has taken on final shape, but not size
   D. If No SRY gene present, then gonads default to ovaries, and internal and external female genitalia

II. Disorders of Sex Development DSD (previously Ambiguous Genitalia) – general concepts
   A. 46 XY DSD
      1. Subnormal Testosterone or DHT (Biosynthetic defect)
      2. Decreased responsivity to Testosterone at receptor (AIS)
   B. 46 XX DSD
      1. Excess Maternal Androgens (e.g. ovarian tumor)
      2. Excess Exogenous Androgens (Progesterone, DHEA, etc)
      3. Excess Fetal Adrenal Androgens (e.g. CAH)
   C. OVOTESTES 46 XX, 46 XY or Mosaicism – VERY RARE
      1. BOTH Ovarian and Testicular tissue present
   D. Big Picture concepts
      1. A block or inability to produce/respond to Testosterone or DHT will cause external genitalia to look less virilized in XY
         a. Androgen Insensitivity Syndrome
         b. 5 Alpha reductase deficiency (can’t make DHT)
      2. Overproduction of androgens will virilize a female
         a. Progesterone/Testosterone
         b. Block in cortisol synthesis => spillover to androgens - CAH

III. Diagnostic Workup/Studies
   A. Palpate for Testicles
   B. Ultrasound – presence of Mullerian or Wolffian structures, ovaries vs testicles
   C. Karyotype – Used as guide further biochemical or genetic testing
      1. Does NOT determine gender of rearing
D. Adrenal Androgens and intermediates (see below- Adrenal sxn)
E. Further workup based on initial findings – Gene testing, etc

IV. Androgen Insensitivity Syndrome – AIS – Androgen Receptor defect
A. Complete AIS 46 XY DSD
   1. External Genitalia Typical Female (No response to T)
   2. Internal Genitalia Typical “Male”
      a. No Uterus or fallopian tubes (presence of AMH)
      b. Testicles present
   3. No development of Pubic hair
   4. + development of Breast Tissue (excess Estrogen)
   5. NO Menses
B. Partial AIS – 46 XY DSD
   1. External Genitalia Ambiguous
   2. Internal Genitalia “male”
   3. some Pubic hair/Axillary hair
   4. +/- development of breast tissue
   5. NO menses
   6. Sex of rearing individualized

V. 5 Alpha Reductase Deficiency
A. Enzyme converting Testosterone => Dihydrotestosterone (DHT)
B. If No Enzyme, No DHT, no virilization at birth=> external female genitalia
C. At puberty, Increasing levels of Testosterone causes virilization.
VI. Congenital Adrenal Hyperplasia – reference

A. Caused by enzymatic block in cortisol (+/- aldosterone) production
   1. Drives increased ACTH production, and subsequently adrenal cortex hyperplasia.
   2. “intermediate” precursors are overproduced, and may cause spillover to Androgen pathway, or shunt away from Androgen pathway-> ambiguity.

B. Multiple possible blocks-can cause DSD with atypical genitals
   1. 21 OH deficiency (see below)- virilizes XX Individual
   2. 11 OH deficiency – virilizes XX Individual
   3. 3 B HSD deficiency – virilizes XX, undervirilizes XY
<table>
<thead>
<tr>
<th>CAH Type</th>
<th>SW?</th>
<th>Ambiguous Genitalia?</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>21α OH Defic Salt Wasting</td>
<td>Yes</td>
<td>Female – Yes Male – No</td>
<td>Adrenal Crisis at 7-14 Days. High Mortality. Most common form</td>
</tr>
<tr>
<td>21α OH Defic Simple Virilize</td>
<td>No</td>
<td>Female – Yes Male – No</td>
<td>Found at birth in female Early adrenarche – male</td>
</tr>
<tr>
<td>21α OH Defic Non-Classical</td>
<td>No</td>
<td>Female – NO Male – N/A</td>
<td>Menstrual Irregularities, Hirsutism–Adolescence</td>
</tr>
<tr>
<td>11β OH Deficiency</td>
<td>Maybe</td>
<td>Female – Yes Male – No</td>
<td>Hypertension from excess DOC if untreated</td>
</tr>
<tr>
<td>3β HS Deficiency</td>
<td>Maybe</td>
<td>Female – Yes Male – YES</td>
<td>Alters genitals in both sexes</td>
</tr>
</tbody>
</table>

C. Diagnostic workup for CAH
   1. Labs baseline and post cortrosyn stimulation test
      a. 17 OHProgesterone
      b. DOC, 17 OHpregnelone
      c. Renin, Aldosterone
      d. DHEA, Androstenedione, ACTH

D. Treatment and Followup
   1. initial/crisis – Fluids!!! N.S. 10- 20 cc/kg/bolus
   2. hydrocortisone with 25 mg IM or IV
   3. Continue at 100 mg/m2/day divided q6 hours
   4. Dextrose for possible hypoglycemia
   5. Taper hydrocortisone (HC) when clinically improved
      a. HC 15-25 mg/m2/day
      b. Fludrocortisone 0.1-0.2 mg/day
   6. Monitor with 17OHP, Androstenedione and Renin levels
OTHER ADRENAL DISORDERS

I. Primary Adrenal Insufficiency – AKA Addison’s Disease
   A. Causes
      1. Autoimmune Destruction: + Adrenal Antibodies
         a. Part of Autoimmune Polyglandular Syndrome (APS) I&II
            • APS 1 due to AIRE gene→Addisons, Mucocutaneous Candidiasis
            • APS 2, Addisons, DM, Hashimotos
      2. Infection - Tuberculosis
      3. Post infection-e.g. meningococcus (Waterhouse Friderichsen)
      4. Adrenal Hypoplasia Congenita (AHC)- underdeveloped adrenal cortex
         a. Due to DAX1 mutation (NR0B1 gene)
         b. Can mimic CAH, but no increased intermediates
         c. Salt-Losing Crisis in Neonatal period
         d. May have LH/FSH deficiency – underdeveloped male
         e. Treat like CAH 21 OH deficiency, but lower doses of hydrocortisone are sufficient
      5. Adrenoleukodystrophy /Adrenomyeloneuropathy .
         a. X-linked –ABCD1 gene
         b. Usually presents as Loss of Milestones- neurologic
         c. Followed by adrenal insufficiency
         d. BMT is only long term cure/option
   B. Symptoms of primary adrenal insufficiency
      1. Near-death experience = hypotension, hyponatremia, hyperkalemia, acidosis, hypoglycemia
      2. weight loss
      3. vomiting
      4. Hyperpigmentation- creases of hands, scars and gums
   C. Treatment
      1. Fluids – Normal Saline and Dextrose
      2. Hydrocortisone 25 mg to 50 mg IV every 6 hours
      3. Once Stable 8-12 mg/m2/day
      4. Fludrocortisone may be required 0.1-0.2 mg/day

II. Cushing Syndrome
   A. Causes
      1. Exogenous Steroids
      2. Excess ACTH production
      3. Adrenal Adenoma/Carcinoma
      4. Ectopic ACTH
   B. Clinical Features
      1. Growth Failure (note, not seen in exogenous obesity)
2. Truncal obesity, acne hirustism, hypertension, striae, osteoporosis,

C. Diagnostic Workup
1. Screen with Overnight Dexamethasone Suppression or:
2. 24 hour urine for Free Cortisol

D. Treatment
1. Remove steroids (usually outside)
   a. Wean Prednisone/Dex if possible
   b. If tumor of pituitary – then resect with risk of panhypopituitarism
   c. If adrenal tumor, then requires care when removing mass – Spill and Seed

III. Pheochromocytoma
A. RARE tumor of Adrenal Medulla
   When Pheochromocytoma present, think of Multiple Endocrine Neoplasia MEN 2A/2B, NF-1, Von Hippel Lindau

B. “Paroxysms” of severe headache and hypertension and sweating
C. Due to excess catecholamines
D. Diagnosis
1. Urinary Metanephrines
2. Plasma Free Metanephrines
3. MRI or CT of Abdomen
4. MIBG scan

E. Treatment
1. Preop – alpha adrenergic blockade
2. Surgical resection

HYPOGLYCEMIA

I. Hypoglycemia – Classically defined
   A. Plasma glucose value of <50 mg/dl after 24 hours of age
   B. Symptoms consistent with inadequate glucose availability
      1. shaky, sweaty, hungry, dizzy, nervous
   C. Resolution of symptoms with normalization of blood glucose.

II. Differential Diagnosis – Neonatal period
   A. Prematurity – inadequate stores
   B. Hyperinsulinism
      1. Infant of a Diabetic Mother=IDM
      2. Malposition of UA catheter
      3. B-cell dysfunction (Hyperinsulinism)
      4. Perinatal Stress/Hypoxia
5. Beckwith Wiedemann Syndrome
   - Big tongue, umbilical hernia
6. Hypopituitarism

III. Differential Diagnosis – **Toddler/child**
A. Ketotic Hypoglycemia (dx of exclusion)
B. Hyperinsulinism
C. Hypopituitarism
D. Metabolic defects
   1. MCAD, GSD (0,1,3,6,9)
E. Liver failure

IV. Endocrine Causes of Hypoglycemia
A. – 4 counterregulatory hormones (increase glucose) and only one “hypoglycemic” hormone - insulin
   1. Cortisol, Growth Hormone, Epinephrine and Glucagon
B. Cortisol Deficiency – 1° (Addison’s) vs Central Pituitary
C. GH Deficiency – Pituitary dysfunction
D. Epinephrine and glucagon deficiencies are rare
E. Hyperinsulinism
   1. Accidental excessive SQ insulin – iatrogenic
   2. Infant of a diabetic mother (IDM)
   3. SGA, Stress/Neonatal Hypoxia
   4. Accidental ingestion of Sulfonylurea agents
   5. NEONATE Excess secretion due to genetic defect
      - Requires glucose infusion at well above physiologic replacement (10-15 mg/kg/min)
      - Large for Gestational Age
      - Seizures
      - Profound early hypoglycemia
      - Occurs both pre and post prandial

V. Critical Sample-obtained after glucose confirmed and before treatment
A. **Paired insulin/glucose**
B. GH and Cortisol
C. Serum Ketones (or urine ketones shortly after event)
D. To Be Complete – Include Lactate, Ammonia and Free Fatty Acids, Urine Organic Acids, Plasma Acylcarnitine profile

VI. Treatment of hypoglycemia – regardless of cause
A. Older child -Alert, interactive -> 10-15 grams of carbs via juice
B. Altered consciousness
   1. **neonate/infants** - 2 cc/kg of D10 over 1-2 minutes
   2. **children** 5 cc/kg of D10
3. glucagon 0.25-1 mg IM

VII. Rules of thumb
A. If hypoglycemia is at random times with respect to food, think Hyperinsulinism
B. If there are no/trace ketones after an event, think insulin or FA oxidation defect
C. If midline defects or nystagmus, think hypopituitarism
D. If hypoglycemia after overnight fast, think hypopituitarism or fatty acid oxidation defect

CALCIUM METABOLISM
I. 3 important Points – (A,B,C)
   A. PTH net effect is to ↑ serum calcium, ↓ serum Phosphorous
   B. Vitamin D ↑'s absorption of both Calcium and Phosphorous
   C. Vitamin D is a feedback inhibitor for PTH
II. PTH increases calcium by 3 mechanisms
   A. ↑'d bone resorption (bone bank)
   B. ↑'d Calcium resorption from kidney (recycling)
   C. ↑'d Vitamin D activation → ↑'d gut absorption of Ca
III. Calcitonin decreases serum calcium
   A. Secreted by C-cells
   B. Blocks osteoclastic resorption of bone -> less serum Ca

IV. Hypocalcemia
   A. Signs and Symptoms
      1. Tetany/Seizure
      2. Chvostek (7th nerve)
      3. Trousseau (BP cuff)
      4. Irritability
   B. Diagnostic workup
      1. iPTH with Calcium
      2. 25-Vitamin D and 1, 25 Vitamin D
      3. Mg and Phosphorous
      4. Urinary Calcium and creatinine
   C. Causes of Hypocalcemia-most common
      1. Hypoparathyroidism/Pseudohypoparathyroidism
         • Failure at 1 of 2 levels – production vs action at receptor (pseudo)
         • Causes of Hypoparathyroidism
            • DiGeorge/Velocardiofacial (VCF) syndrome
               ♦ Deletion of 22q11 region
               ♦ Cardiac Defects
Daniels, MW  
Endocrinology

- Palatal defects
- Broad nose, long fingers
- T-cell dysfunction (DiGeorge) – infections
- CHARGE association
- Autoimmune Polyglandular Syndrome I/II
- Familial Hypoparathyroidism (Autosomal DOM)
- **Cause of pseudo hypoparathyroidism - Albright**
- **Hereditary Osteodystrophy - AHO (Pseudo or pseudo-pseudo)**
- ![AHO = Albright's Hereditary Osteodystrophy](chart)

AHO = Albright's Hereditary Osteodystrophy

2. Causes of Vitamin D Deficiency
   a. Decreased intake
      - Breast fed/non-standard formula fed
      - No supplementation
   b. Decreased absorption
      - Fat Malabsorption (ADEK)
   c. Decreased production
      - No Sun
      - Skin pigmentation prevents UV rays to cross
      - Excessive use of sunscreen (heliophobia)
   d. Leads to RICKETS

<table>
<thead>
<tr>
<th>Calcium/Phos Abnl</th>
<th>Calcium</th>
<th>Phosphorous</th>
<th>Intact PTH</th>
<th>AHO?</th>
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<td>↓</td>
<td>No</td>
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<tr>
<td>Ψ hypoparathyroidism</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Yes</td>
</tr>
<tr>
<td>ΨΨ hypoparathyroidism</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>Yes</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>↓</td>
<td>↓ or Nl</td>
<td>Nl or ↑</td>
<td>No (but rickets)</td>
</tr>
</tbody>
</table>

1. Rickets – Bowed legs, ragged and widened metaphyses
   a. Nutritional = Vitamin D deficiency
      - ![PREVENTION](chart)
        supplement all Breastfed babies with 400 IU Vit D/day starting first 2 months-continued while breastfeeding
      - ![Treatment](chart)
        Treatment – 1000 IU Vit D or more. May need calcitriol – Quicker effect
   b. Hypophosphatemic Rickets - GENETIC
      - X-linked- GENETIC
      - Low Serum Phos, High Urine Phos,
      - Normal Calcium, high Alk Phos
      - Normal Vitamin D levels
      - Treatment with Phos and calcitrol
II. Hypercalcemia

A. Symptoms
   1. Polyuria
   2. Nephrolithiasis (STONES)
   3. Bone Pain (BONES)
   4. Depression (PSYCHIC MOANS)
   5. Ulcer/Nausea (ABDOMINAL GROANS)

B. Diagnostic Workup for Hypercalcemia
   1. iPTH (with Calcium)
   2. 25-Vitamin D and 1, 25 Vitamin D
   3. Mg and Phosphorous
   4. Urinary Calcium

C. Causes

<table>
<thead>
<tr>
<th>Cause</th>
<th>Ca</th>
<th>PO4</th>
<th>iPTH</th>
<th>UCa</th>
<th>Notes</th>
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<tr>
<td>Hyperparathyroid</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>May be part of MEN 1 and 2A</td>
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<tr>
<td>Parathyroid Adenoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTHrP</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Usually with solid Tumor. Low iPTH.</td>
</tr>
<tr>
<td>Hypervitaminosis D</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Excessive ingestion</td>
</tr>
<tr>
<td>Benign Familial Hypercalcemia</td>
<td>↑</td>
<td>NL</td>
<td>NL</td>
<td>↓</td>
<td>Hypocalciuria is notable finding. CaSR gene</td>
</tr>
</tbody>
</table>

D. Treatment
   1. Hydration with IV fluids
   2. Furosemide
   3. Glucocorticoids
   4. Calcitonin
   5. Bisphosphonates
GROWTH

I. Tidbits
   A. “Normal” is defined by us as +/- 2 S.D. from mean
   B. Average Birthweight is about 3.2 kg
   C. Babies double weight by 4 months, triple by a year (10 kg at 1 year is average)
   D. Growth Velocity—“Rule of 24” Year x Velocity ~ 24 for first 3 yrs
      1. 1st year is 25 cm/yr
      2. 2nd year is 12 cm/yr
      3. 3rd year is 8 cm/yr
      4. Puberty peak is 10 cm/yr boys, 8 cm/year girls

II. Short Stature and Growth Failure
   A. Workup is begun when
      1. Percentiles are crossed after age 2
      2. Height is <3rd percentile
   B. Diagnostic Workup - Initial
      1. Growth Velocity
      2. General Chemistry Panel, ESR, Celiac screen
      3. TSH
      4. IGF-1 and IGF-BP3
      5. Bone Age
   C. Common Causes
      1. Constitutional Delay of Growth and Puberty
         a. “Late Bloomer”
         b. Normal Laboratories
         c. Delayed Bone Age
         d. Otherwise Healthy
      2. Familial (Genetic) Short Stature
         a. Most common cause (up to 3% of normal population)
         b. Calculation of Midparental height (MPH)
            • MPH for Males = (Moth Ht + 13 cm + Fath ht)/2
            • MPH for Females = (Fath Ht – 13 cm + Moth ht)/2
            • 2 SD will be +/- 10 cm
         c. “Familial” short stature may be caused by genes – be cautious
            • HESX1, PROP1, POUF1, GHR, And MORE
      3. Chronic Inflammation/Illness
         a. JRA, IBD, Cardiac disease, Renal disease/RTA
      4. Malabsorption/Malnutrition (e.g. celiac sprue)
      5. Hypothyroidism
      6. Cushing’s Syndrome (Use of Glucocorticoids)
      7. Growth Hormone Deficiency (GHD)
         a. Less than 1 in 5000 children have isolated GHD
b. In the complete form, may show up as recurrent low blood sugar in infancy

c. Growth usually slows after 6 months

d. Often after Cranial irradiation, surgery or trauma.

e. Diagnostic Hints/Tools – RULE OUT OTHER CAUSES
   - Current height
   - **Growth Velocity – FALLING FROM CURVE**
     - Insulin-Like Growth Factors (IGF-1 and IGF-BP3)
     - Bone Age of hand/wrist
       - Delayed in many disease states, so not specific
   - GH stimulation tests
     - Arginine, Clonidine, Insulin, Exercise…etc.
   - Pituitary MRI

f. **Growth Hormone Therapy**
   - Injectable only (SQ) DAILY – 0.025 -0.05 mg/kg/day
   - Side Effects – (Head, Shoulders, Knees and Hips)
     - Benign Intracranial Hypertension (Pseudotumor Cerebri)
     - Scoliosis (association or causation)
     - SCFE
     - Associated with Thyroid and Cortisol deficiencies
     - ?Increased risk of Colon CA/Bone Tumor/Intracranial bleed?

8. Syndromic Short Stature
   a. Trisomy 21 (Genetics Lecture)
   b. Turner Syndrome 45 XO, AND variants
      - Left Sided Heart defects
      - Absent Pubertal Development/infertility
      - Edema at birth
      - Low Hairline/Webbed neck
      - Abnl carrying angle
      - Shield Chest
      - Horseshoe Defect
      -
   c. Noonan (PTPN11 defect in 50%, SOS1 in 20%, Others)
      - Short stature
      - Low hairline
      - Shield chest
      - Right sided heart defects (PS)
      - NO renal defects
d. Prader Willi Syndrome (PWS) 15q11-imprinting
   • Short Stature
   • Developmental Delay
   • Morbid Obesity/hyperphagia
   • Hypogonadotropic Hypogonadism
     ♦ small phallus, small testicles, pubertal delay

e. Russell-Silver (IUGR/SGA)
   • Small at birth
   • Limb Assymetry
   • Triangular head
   • Cryptorchidism
   • No Catch up growth (born small/stay small)

III. Tall Stature
   A. Klinefelter (47XXY)
   B. Marfan
   C. Homocystinuria
   D. Hyperthyroidism
   E. GH excess (Gigantism)
   F. Precocious puberty (but Tall stature →Short adult height)
   G. Soto Syndrome (cerebral gigantism)

PUBERTY/GONADAL FUNCTION

I. Defined:
   A. The development of 2° sexual characteristics, including breasts, ↑testes, pubic hair, axillary hair, facial hair, acne and menses
   B. Adrenarche (AKA Pubarche) - The development of pubic hair and acne secondary to adrenal androgens
   C. Thelarche - The development of breast tissue
   D. Gonadarche – The enlargement of the testicles or ovaries

II. Normal puberty
   A. GnRH secreted from Hypothalamus →LH/FSH – pulsatile
      1. LH→ testosterone and ovarian androgens
      2. FSH→ estrogen production and inhibin
      3. E2 and inhibin feed back on Hypothalamus/Pituitary
   B. Early mini-puberty for both sexes
      1. Estrogen production and small amount of breast development.
         a. Benign premature thelarche – Breast tissue can be normal up to age 18-24 months if not rapid progression
      2. Testosterone production in Utero and postnatally
         a. Measurable Testosterone, + erections
   C. Female Tanner Staging
      1. I – prepubertal  No tissue
      2. II small amount of subareolar tissue
      3. III increased breast tissue with no contour from areola to breast
4. IV areola forms mound on breast tissue
5. V breast tissue with no contour to areola-adult

D. Typical female development – TAG-Me
1. Thelarche = Breast development First sign of puberty in 90% - (7–13* )
2. Adrenarche = Pubic hair follows (or precedes) shortly (age 9 – 13)
3. Growth spurt usually starts in the year after breasts first develop, and peaks while breasts are Tanner II –III
4. Menarche (commencement of Menses) occurs ~ 2 years after start of puberty
   a. Average age is 12 – 12.5 years

E. Typical Male development
1. Testicular enlargement is seen first
2. Enlargement to 4cc = Tanner 2
3. average age is 11½, range is 9 -14
4. Pubic Hair follows 6 months -1 year later
5. Penile enlargement
6. Growth spurt in Tanner stage III-IV (later than females)
7. Axillary hair follows (avg. 14), then facial hair (avg. 15)
8. Total time is 3¼ years average
9. Order is T - H - P -G –A

III. Precocious Puberty – Central vs Peripheral – Early start of sexual characteristics
A. Start of sex characteristics before 7 (?8) for female or 9 - male
B. Diagnostic Workup
1. Baseline labs
   a. LH, FSH, Estradiol/Testosterone
   b. Bone Age (often advanced 2-3 years)
2. If baseline labs inconclusive: Leuprolide stimulation test
   a. Rise in LH indicates CPP
   b. No rise suggests benign premature thelarche
   c. Supression of LH and FSH suggests Peripheral
C. Central precocious puberty (CPP)
1. Causes
   a. Idiopathic - benign
   b. Intracerebral cause
      • CP, hydrocephalus, trauma, irradiation, tumors (germinoma, astrocytoma), Hamartoma (Pallister Hall syndrome), Neurofibromatosis-1
2. Girls - 95% are idiopathic
3. Boys-majority are NOT idiopathic
D. Peripheral (pseudoprecocious) puberty
   1. Will see Low LH, FSH and HIGH Testosterone or Estradiol
   2. Causes
      a. Familial Male Gonadotropin-independent PP
         • Constitutively active LH receptor
         • BOYS ONLY
      b. McCune Albright Syndrome - G-protein abnl
         • Triad of Café-au-lait, Fibrous Dysplasia, Precocious puberty
         • Girls>Boys
      c. Congenital Adrenal Hyperplasia
         • Adrenarche, not thelarche
      d. Exposure to Exogenous Steroids
         • Testosterone gel
         • Estrogen creams

E. Treatment
   1. Central Precocious Puberty
      a. Leuprolide or Histrelin - (GnRH) superagonists
         • Continuous administration → downregulation of GnRH receptor
         • Annual Implant vs Monthly Depot vs daily SQ vs intranasal
         • Treatment of social benefit and maintaining height
   2. Peripheral
      a. Depends on source of hormone... remove offending agent if possible
      b. Block Effects of Sex Hormones
         • Androgen receptor blockers (Bicalutamide)
         • Estrogen Receptor Blocker (Tamoxifen)

IV. Delayed Puberty
A. Defined as NO secondary sexual development by age 13 in girls, 14 in boys
B. Diagnostic Workup
   1. Baseline labs
      a. LH, FSH, Estradiol/Testosterone
      b. TSH
      c. Chemistry panel, ESR
      d. Bone Age (often delayed 2-3 years)
C. Nonendocrine Causes
   1. Constitutional Delay in growth/puberty
      a. “Late Bloomer”
      b. Normal Birth weight, No chronic illness
Daniels, MW Endocrinology

2. Chronic Illness
   a. CF, JRA, Crohn’s
   b. Hypothyroidism

D. Endocrine Causes of Pubertal delay
   1. Hypogonadotropic hypogonadism (i.e. “Something’s Wrong with the Pituitary”)
      a. **Isolated deficiency**
         - normal height pre-adolescence
         - no growth spurt
         - may have adrenarche
         - if associated **anosmia** ***Kallmann syndrome***
      b. Congenital Panhypopituitarism
         - Septo-optic dysplasia (SOD)
         - Empty sella syndrome
   c. CNS tumors
      - Craniopharyngioma
      - Germinoma
      - Histiocytosis X, Granulomatous infection
      - CNS irradiation, CNS trauma
   d. Genetic Syndromes
      - Prader Willi Syndrome
      - Leptin Deficiency

2. **HYPERgonadotropic hypogonadism** (i.e. “Something’s wrong with the gonads”)
   a. Mumps Orchitis
   b. Turner Syndrome (45 XO) (see info in Growth sxn)
   c. Functional Ovarian Failure
   d. Trauma, Chemo, Gonadal removal
   e. Klinefelter Syndrome (47 XXY)
      - 47 XXY
      - 1:500 live male births
      - Tall Stature and Eunuchoid proportions
      - Gynecomastia
      - Stalled puberty (can get to Tanner 3-4)
      - Testicles noted to be small only after puberty starts… firm
   f. If elevated FSH -> Karyotype (45X, 47XXY)
   g. If concern of CNS lesion – MRI of pituitary
3. Treatment
   a. Replacement of Sex Steroids
      • Girls – Estrogen
         ♦ Patch, Premarin, Oral Estradiol (controversial)
         ♦ OCP’s
      • Boys - Testosterone
         ♦ patch, gel, injection

ICON GLOSSARY

= Don’t Forget - This may come in handy!
= Primary Treatment Option
= Think About This Option if you see associated Features
= First Choice for Workup Options
One Line Clinical Scenarios – courtesy of Dr. Nakamoto

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Week old Male with FTT, persistent vomiting, dehydration, acidosis</td>
<td>CAH 21OH deficiency</td>
</tr>
<tr>
<td>Inguinal hernia, primary amenorrhea, no pubic hair</td>
<td>Androgen Insensitivity Syndrome</td>
</tr>
<tr>
<td>11 y.o. Female with ambiguous genitalia, masculinizes at puberty</td>
<td>5 Alpha Reductase def.</td>
</tr>
<tr>
<td>3 day old baby, 10 lbs at birth, jittery</td>
<td>Infant Diabetic Mother with hypocalcemia</td>
</tr>
<tr>
<td>5 day old baby, small jaw, broad nose, Tetralogy of Fallot, seizure</td>
<td>DiGeorge/VCF</td>
</tr>
<tr>
<td>8 y.o. boy with Dev Delay, short, round facies, SQ calcifications,</td>
<td>Albright’s Hereditary Osteodystrophy/Ψhypopara</td>
</tr>
<tr>
<td>3 month old male with elfin facies, supravalvular aortic stenosis,</td>
<td>William’s Syndrome</td>
</tr>
<tr>
<td>4 day old male with hypoglycemia, omphalocele, hemihypertrophy</td>
<td>Beckwith Wiedemann Syndrome</td>
</tr>
<tr>
<td>10 pound plethoric neonate, requiring 15 mg/kg/min dextrose infusion.</td>
<td>Congenital hyperinsulinism</td>
</tr>
<tr>
<td>18 month old boy with mild fever overnight, presents with loss of</td>
<td>Ketotic hypoglycemia (DX OF EXCLUSION)</td>
</tr>
<tr>
<td>5 day old male with small phallus, jaundice, now with glucose of 45</td>
<td>Hypopituitarism (ACTH, GH deficiency)</td>
</tr>
<tr>
<td>9 year old male &lt;3%ile, following “own curve”, delayed bone age of</td>
<td>Constitutional Delay of Growth and Puberty</td>
</tr>
<tr>
<td>6 year old with nighttime headaches, falling from 20th to 5th</td>
<td>Intracranial Tumor in region of Pituitary</td>
</tr>
<tr>
<td>9 month female who has dropped from 50th to 25th percentile for</td>
<td>NORMAL</td>
</tr>
<tr>
<td>18 month male, length and weight “stalled” since 9 months. Stools</td>
<td>Celiac/malabsorption</td>
</tr>
<tr>
<td>11 year old female with no growth x 2 years, tired, constipated and</td>
<td>Hypothyroidism-likely Hashimoto’s</td>
</tr>
<tr>
<td>13 year old female, &lt;=3%ile, no breast development. History of heart</td>
<td>Turner Syndrome</td>
</tr>
<tr>
<td>2 year old female with Bilateral Breast buds, unchanged x 1 year, no</td>
<td>Benign Premature Thelarche</td>
</tr>
<tr>
<td>5 year old girl with pubic hair, mild hyperpigmentation of skin folds,</td>
<td>Simple virilizing CAH -21 OH deficiency</td>
</tr>
<tr>
<td>14 year old girl, school troubles, getting in fights, appears to be</td>
<td>Graves Hyperthyroidism</td>
</tr>
<tr>
<td>14 year old boy, tall, thin, mid-puberty but small testicles noted</td>
<td>Klinefelter Syndrome</td>
</tr>
<tr>
<td>4 year old girl with rapid breast development, large brown birthmark,</td>
<td>McCune Albright syndrome</td>
</tr>
</tbody>
</table>
Laundry List of Endocrine Diseases and Syndromes on the Boards

Growth
- GH Deficiency
- Hypothyroidism
- Turner Syndrome
- SHOX deficiency
- Constitutional Delay of Growth and Puberty
- Familial/Genetic Short Stature
- Russell-Silver Syndrome/SGA
- Down Syndrome
- Marfan Syndrome
- Klinefelter Syndrome (47XXY)
- Homocystinuria
- GH Excess (Gigantism)
- Sotos Syndrome (Cerebral Gigantism)

Puberty
- Central Precocious Puberty – idiopathic
- Familial male-limited gonadotropin independent Precocious Puberty
- McCune Albright (classic triad)
- Congenital Adrenal Hyperplasia
- Adrenal/Ovarian/Testicular tumor
- Constitutional Delay of Puberty
- Turner Syndrome (primary gonadal failure)
- Klinefelter Syndrome
- Kallman Syndrome (anosmia + hypogonadotropism)
- Prolactinoma – Amenorrhea/galactorrhea

Thyroid
- Congenital Hypothyroidism
- Autoimmune hypothyroidism (Hashimoto’s)
- Autoimmune Hyperthyroidism (Graves)
- Central hypothyroidism (TSH deficiency)

Adrenal
- Congenital Adrenal Hyperplasia
- 21 OH deficiency
- 11 B OH deficiency
- Adrenal Hypoplasia Congenita (DAX1 mutation)
- Adrenoleukodystrophy (Lorenzo’s Oil)
- Addison Disease (Autoimmune adrenalitis)
- Waterhouse-Friderichsen (post-infection hemorrhage)
- Cushing Disease (pituitary ACTH excess)
- Cushing Syndrome (Cortisol excess, any source)
- Pheochromocytoma

Ambiguous Genitalia
- Congenital Adrenal Hyperplasia
- Androgen Insensitivity Syndrome
- 5 Alpha-Reductase Deficiency
- Maternal exposure to androgens
- True Hermaphroditism
- Hypopituitarism (n.b. normally formed phallus, but small)
- Smith-Lemli-Opitz syndrome
- Denys-Drash syndrome

Calcium
- Hypoparathyroidism
  - Transient neonatal
  - DiGeorge/VCF (22q11 or 10p-)
  - Mitochondrial disorders (KSS)
- Pseudohypoparathyroidism/Albrights
- Hereditary osteodystrophy
- Vitamin D Deficiency Rickets
  - 1 alpha hydroxylase deficiency
- Hypophosphatemic Rickets
- Hyperparathyroidism
  - Part of MEN I and IIa

Hypoglycemia
- Hyperinsulinism (neonatal)
  - SUR/KIR defect
  - Hyperinsulinism/Hyperammonemia syndrome
  - Infant of a Diabetic Mother
  - IUGR/SGA
- Hypopituitarism
  - GH deficiency
  - ACTH/Cortisol deficiency
- Ketotic hypoglycemia
  - Insulin-induced or Med induced

Sodium/Water Balance
- Diabetes Insipidus – Central
- Diabetes Insipidus – Nephrogenic
- SIADH
  - Cerebral Salt Wasting
  - Psychogenic Polydipsia
- Mineralocorticoid deficiency/resistance

Miscellaneous
- Gynecomastia (>50% boys – usually benign)
- Idiopathic Juvenile Osteoporosis
- Osteogenesis Imperfecta Types I – VI
- Diabetes Mellitus – Other Lecture