ADRENAL
Congenital Adrenal Hyperplasia (CAH)

- group of autosomal recessive disorders affecting adrenal steroidogenesis
  - 21-Hydroxylase deficiency
  - 11β-Hydroxylase deficiency
  - 17α-Hydroxylase deficiency
  - 3β-Hydroxysteroid dehydrogenase deficiency
  - Lipoid/StAR CAH

- U.S. Occurrences – 1:15,500 Caucasian births, 1:42,000 African American births
Regulates glucose (blood sugar) levels
Increases fat in the body
Helps to defend the body against infection
Helps the body respond to stress
Enzyme pathway

Cholesterol

Progesterone  17α-Hydroxyprogesterone  → ANDROGENS

21-Hydroxylase

Aldosterone  Cortisol
**Pathophysiology in Classic, Salt-Wasting CAH 21-OH Deficiency**

**VIRILIZATION**
(of females)

- Cholesterol → Pregnenolone → 17-Hydroxyprogrenolone → 17-Hydroxypregnenolone → Androsterone
- 3β-dehydrogenase

- Progesterone → 17-Hydroxyprogesterone → Androstenedione
- 3β-dehydrogenase

- Deoxy cortisol → 11β-Hydroxylase → Corticosterone → 18-Hydroxycorticosterone → Aldosterone
- 18-hydroxylase

- 11-Deoxycorticisol → 11β-Hydroxylase → Cortisol

**Hypotension, hypoglycemia, shock**

**Salt-loss, hyperkalemia**

- Terminal (in the testes)

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**Images**

- Image of a medical diagram showing the metabolic pathways involved in classic salt-wasting CAH 21-OH deficiency.

- Image of a medical condition illustrating virilization in females, typically demonstrated by changes in secondary sex characteristics.

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**Note:**

- Detailed metabolic pathways and their respective enzymes are labeled in the diagram, illustrating the specific defects in cortisol metabolism.

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**Explanation:**

- The diagram outlines the metabolic pathways affected in classic salt-wasting congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, leading to excess production of androgens in females and salt-wasting in males.

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**Key Points:**

- Cholesterol is converted to pregnenolone, which is further processed to 17-hydroxyprogrenolone and then to 17-hydroxypregnenolone.

- Progesterone undergoes similar conversions to 17-hydroxyprogesterone, leading to the production of androsterone.

- The pathway also shows deoxycorticosterone and aldosterone production, indicating the role of 18-hydroxylase and 11β-hydroxylase enzymes.

- The diagram highlights the terminal changes in developing fetuses, typical for virilization in females, showing the development of secondary sex characteristics.

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**Further Reading:**

- Detailed discussions on the metabolic pathways and clinical manifestations of classic salt-wasting CAH.

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**Image Credits:**

- Diagram and images provided for educational purposes, linking to detailed medical resources for further study.

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**Conclusion:**

- The diagram effectively communicates the complex metabolic changes in classic salt-wasting CAH, emphasizing the role of enzymes and their respective metabolic pathways.

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**Additional Information:**

- For a comprehensive understanding, consulting medical literature on congenital adrenal hyperplasia is recommended.

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**Table of Enzymes and Pathways:**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>3β-dehydrogenase</td>
<td>Cholesterol → Pregnenolone → 17-Hydroxyprogrenolone → 17-Hydroxypregnenolone → Androsterone</td>
</tr>
<tr>
<td>18-hydroxylase</td>
<td>Deoxycorticosterone → 18-Hydroxycorticosterone → Aldosterone</td>
</tr>
<tr>
<td>11β-hydroxylase</td>
<td>11-Deoxycorticisol → Cortisol</td>
</tr>
</tbody>
</table>

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**Clinical Implications:**

- Early diagnosis and treatment are crucial to prevent long-term complications.

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**References:**


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**Image Sources:**

- Medical diagrams sourced from reputable medical journals and educational resources.
Classic 21-Hydroxylase Deficiency Exam

Findings

**Females**
- Enlarged clitoris
- Partly-fused, rugose labia majora
- Common urogenital sinus in place of urethra and vagina
- Salt-losing present soon after birth, given ambiguous genitalia
- Normal internal female organs

**Males**
- Subtle hyperpigmentation
- Possible penile enlargement
- Salt-losing presents DOL 7-14 with emesis, weight loss, lethargy, dehydration, shock, hyponatremia, hyperkalemia
- Non-salt-losing present with early virilization at 2-4 yrs
- Normal male internal organs, but can have small testes if untreated.
Salt-Wasting 21-Hydroxylase Deficiency

- 67% patients with classic 21-hydroxylase deficiency
- Secondary to aldosterone deficiency
  - Associated lab abnormalities: hyponatremia, hyperkalemia
- Early signs: frequent feedings
- Present with salt-wasting and acute adrenal crisis within weeks after birth
Diagnosis

- **17α-hydroxyprogesterone**
- Serum androstenedione (high)
- The biochemical abnormalities in salt losers are:
  - Low plasma sodium
  - High plasma potassium
  - Metabolic acidosis
  - Hypoglycaemia
**Newborn Screen**

- Measures 17OHP on dried blood spot on filter paper
- Need to do after 24 hrs old because 17OHP is high in cord blood and falls to normal newborn levels after 12-24 hours (ideally between 48 and 72 hours)
  - Too early newborn screen, severe stress, prematurity can all have persistently elevated 17OHP and false positive NB screen
  - False negative NB screen occasionally in infants with simple virilizing form or in mothers treated w/glucocorticoids
DIAGNOSIS OF CAH--LATE ONSET CAH

- **ACTH stimulation test**
- Measure 17OHP and other adrenal steroids before and 60 min after IV synthetic ACTH) 17OHP will increase (over 1000 ng/dl)
- Ratios of precursors to products of enzyme activity will be high (over 40)
MANAGEMENT OF

Classic/Salt-wasting CAH

- **Hydrocortisone**
- **Fludrocortisone**

Infants have more renal resistance to aldosterone so usually need higher doses of fludrocortisone than older children and adults.

- **Salt supplements**

Usually only infants need this. Older children are better able to respond to fludrocortisone and are better able to supplement diet with salt if needed.

- **STRESS DOSING:**

  mimic normal physiological response to stress with extra hydrocortisone

**Medical Alert Bracelets**
Affected females will sometimes require corrective surgery to their external genitalia within the first year but as they have a uterus and ovaries they should usually be reared as girls and are able to have children. Definitive surgical reconstruction is usually delayed until late puberty.
Management

- insufficient hormone replacement results in increased ACTH secretion and androgen excess, which will cause rapid initial growth and skeletal maturation at the expense of final height; excessive hormonal replacement will result in skeletal delay and slow growth.
STRESS DOSING

- Higher doses of hydrocortisone
- Try to mimic normal physiological response to stress with extra hydrocortisone
- Stress dose for febrile illness, GI illness with dehydration, unable to take oral feedings, after trauma, before surgery with general anesthesia
GROWTH AND PUBERTY
GROWTH

• Growth Velocity
  – It is the most important tool in early detection of abnormal growth
  – Crossing percentiles on the height or length for age growth chart → demands evaluation even when height still within normal range
Growth Velocity

- Birth-1 year: ≈ 25 cm/year
  - Crossing percentiles toward parents genetics 9-12 mo

- 1-3 years: 1-2 years → ≈ 12.5 cm/year
  - Growth deceleration
  - 2-3 years → ≈ 8 cm/year

- 3 years-Puberty: ≈ 5-6 cm/year
  - Steady growth velocity during childhood

- Adolescence: Up to ≈ 15 cm/year
  - Return of rapid growth
Figure 11.1 Male and female height velocity charts (50th percentile) showing the determinants of childhood growth. The fetal and infantile phases are mainly dependent on adequate nutrition, whereas the childhood and pubertal phases are dependent on growth hormone and other hormones. Adult males are taller than females as they have a longer childhood growth phase, their peak height velocity is higher and their growth ceases later.
Figure 11.2 Measuring height accurately in children.

- Calibration checked
- Head straight, eyes and ears level
- Gentle upward traction on mastoid process
- Knees straight
- Barefoot, with feet flat on floor
- Heels touching back of board
Figure 11.3 Measuring length in infants and young children. An assistant is required to hold the legs straight.
Figure 11.8 X-rays of the left wrist and hand to determine bone ages. This technique allows assessment of skeletal maturation from the time of appearance or maturity of the epiphyseal centres, using a standardised rating system. The child's height can be compared with skeletal maturation and an adult height prediction made. The ages show bone age of each X-ray.
MIDPARENTAL HEIGHT:

GIRLS:
(father’s height − 13) + mother’s height / 2

BOYS:
Father’s height + (mother’s height + 13)/2

The parents height are in cm

TARGET HEIGHT:
Midparental height +/- 2SD (10cm)
Causes & evaluation of short stature

(a) Familial
  - Following growth centile within predicted range for parental height

(b) Severe intrauterine growth restriction or prematurity
  - Short from birth
Diagnostic Approach to the Short Child

- CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY (CDGP)
  - Family history of growth and pubertal delay
  - Delayed bone age
  - Linear growth is below but parallel to the lower percentiles of the growth curve
  - GH and thyroid studies are usually normal
  - Normal final adult height
  - Low dose testosterone therapy (social stress) or observation
(c) Constitutional delay of growth and puberty

Short stature accentuated by delayed puberty. Delayed bone age
Growth Hormone Deficiency

- **Diagnosis**
  - Height or length >3 SD below the mean
  - Slow growth velocity (<5 cm per year)
  - Delayed bone age
  - Low IGF-1 and low Insulin-like growth factor binding protein-3 (IGFBP-3)
  - Provocative test. “GH <10ng/ml in 2 provocative tests”
(d) Endocrine
- growth hormone deficiency
- hypothyroidism
- steroid excess
  - iatrogenic
  - Cushing syndrome
  - IGF-1 deficiency

Falling off height centiles.
Weight centile >height centile.
Short and overweight Markedly delayed bone age.
<table>
<thead>
<tr>
<th></th>
<th>Constitutional Delay</th>
<th>Familial Short Stature</th>
<th>Growth Hormone Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth curve</td>
<td>Growth velocity along or parallel to the lower percentiles of the growth curve.</td>
<td>Growth velocity is parallel to but below the normal growth curve</td>
<td>Height or length &gt;3 SD below the mean</td>
</tr>
<tr>
<td>Family history</td>
<td>Positive late bloomers</td>
<td>One or two parents are short</td>
<td>Depends on the cause</td>
</tr>
<tr>
<td>Bone age</td>
<td>Delayed</td>
<td>Equal to chronological age</td>
<td>Delayed</td>
</tr>
<tr>
<td>Hormonal studies</td>
<td>Normal</td>
<td>Normal</td>
<td>Low IGF-1, and low IGFBP-3</td>
</tr>
<tr>
<td>Sexual Development in Boys</td>
<td>Sexual Development in Girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlargement of testis &gt;3ml or 2.5cm</td>
<td>Breast buds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pubic hair</td>
<td>Pubic hair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height acceleration occurs late at SMR 4-5 (typically age 13-14)</td>
<td>Height acceleration peak during SMR 2-3 (typically 11-12 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Menarche takes usually 2-2 ½ years after breast development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMR</td>
<td>PUBIC HAIR</td>
<td>BREASTS</td>
<td>PENIS</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Pre-pubertal</td>
<td>Pre-pubertal</td>
<td>Pre-pubertal</td>
</tr>
<tr>
<td>2</td>
<td>Sparse, lightly pigmented</td>
<td>Small mound and areolar diameter increases</td>
<td>Scrotum and penis enlarge slightly</td>
</tr>
<tr>
<td>3</td>
<td>Increased in amount, darker, start curling</td>
<td>Breast and areola are larger, no separation of breast contour is noted</td>
<td>Testes and scrotum continue to grow</td>
</tr>
<tr>
<td>4</td>
<td>Abundant, coarse, curly but less than adult</td>
<td>Areola and papilla form secondary mound, separation from contour is noted</td>
<td>Larger and darker scrotum, and penis and in width</td>
</tr>
<tr>
<td>5</td>
<td>Adult pattern extends to medial thigh</td>
<td>Mature; areola become part of general breast contour, more projection of papilla</td>
<td>Adult size scrotum and penis</td>
</tr>
</tbody>
</table>
1.7 Orchidometer to assess testicular volume
Precocious puberty is the onset of pubertal development at an earlier age than expected based upon established normal standards.

Precocious puberty is usually defined as the onset of secondary sexual development before the age of eight years in girls and nine years in boys. These limits are chosen to be 2.5 to 3 SD below the mean age of onset of puberty.
Causes of precocious puberty

Gonadotropin-dependent (LH > FSH)
- Pituitary
  - Gonad enlarges
  - LH ++ FSH +
  - Oestrogen from ovary ++
  - Testosterone from:
    - testis ++
    - adrenal +
  - Pubic hair growth, acne, body odour

Gonadotropin-independent (FSH, LH)
- Pituitary
  - Gonad shrinks or enlarges
  - Feedback
  - LH ↓ FSH ↓
  - Oestrogen
  - Breast enlargement
  - Testosterone
  - Ovarian or extra-gonadal source

Gonadotropin-dependent (LH > FSH)
- Idiopathic/familial
- CNS abnormalities
  - Congenital anomalies, e.g. hydrocephalus
  - Acquired, e.g. post-irradiation, infection, surgery
  - Tumours, e.g. microscopic hamartomas
- Hypothyroidism

Gonadotropin-independent (FSH, LH)
- Rare.
- Adrenal disorders – tumours, congenital adrenal hyperplasia
- Ovarian – tumour (granulosa cell)
- Testicular – tumour (Leydig cell)
- Exogenous sex steroids
PRECOCIOUS PUBERTY

• Precocious puberty in girls < 6-8 years (consider ethnicity)
  – Breast enlargement, which may initially be unilateral.
  – Pubic and axillary hair may appear before
  – Growth spurt and bone age advancement
PRECOCIOUS PUBERTY

- For boys < 9 years is considered precocious.
- Causes:
  - Tumors (e.g., astrocytoma)
  - Hypothalamic hamartomas
  - Acquired CNS injury e.g. inflammation, surgery, trauma
  - Congenital anomalies (e.g., hydrocephalus)
  - Adrenal tumor, CAH
  - Drugs e.g., exposure to testosterone or estrogen
**PREOCIOUS PUBERTY**

**Diagnosis**

- Testosterone level is useful in boys with suspected precocious puberty
- DHEA-S is usually elevated in boys and girls with premature pubarche
- Central precocious puberty may be confirmed by measuring LH levels 60 minutes after stimulation with a GnRH analog
- Bone age (advanced)
- MRI should part of evaluation for boys.

**Management**

- Surgical resection of tumor, and irradiation
- GnRH analog
THYROID
Congenital hypothyroidism

- Thyroid dysgenesis/agenesis
- Prevalence 1 in 4,000 [Whites 1 in 2,000; Blacks 1 in 32,000]
- 2:1 female to male ratio
- Clinical features include: hypotonia, enlarged posterior fontanelle, umbilical hernia, indirect hyperbilirubinemia
- Laboratory findings: Very high TSH and low T4
- Therapy: Thyroxine – keep TSH in normal range
## Clinical features of hypothyroidism

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually asymptomatic and picked up on screening. Otherwise: Failure to thrive Feeding problems Prolonged jaundice Constipation Pale, cold, mottled dry skin Coarse facies Large tongue Hoarse cry Goitre (occasionally) Umbilical hernia Delayed development</td>
<td>Females &gt; males Short stature/growth failure Cold intolerance Dry skin Cold peripheries Bradycardia Thin, dry hair Pale, puffy eyes with loss of eyebrows Goitre Slow-relaxing reflexes Constipation Delayed puberty Obesity Slipped upper femoral epiphysis Deterioration in school work Learning difficulties</td>
</tr>
</tbody>
</table>

![Untreated congenital hypothyroidism.](image)
CONGENITAL HYPOTHYROIDISM

Clinical Manifestations
1. Jaundice
2. Poor muscle tone
3. Low body temperature
4. Long protruding tongue
5. Large anterior fontanel
6. Umbilical hernia
HYPOTHYROIDISM

- The most common cause of preventable mental retardation in children
- Diagnosis is easy & early treatment is beneficial
CONGENITAL HYPOTHYROIDISM

- Laboratory
  - High TSH and low free T4
  - No imaging study is necessary by most experts
6 month female with congenital hypothyroidism...following 4 months therapy
CONGENITAL HYPOTHYROIDISM

• **Treatment**
  - Levothyroxine given orally is the treatment of choice
  - 10-15 micrograms/kg/day initial dose
  - No liquid preparations of levothyroxine should be given to neonates or infants.
  - Crush and mix with water, breast milk .. Never mix with soy milk formula
  - Iron, Ca interfere with absorption
  - If missed one dose give double second day. —goal total 7 doses per week

• **Prognosis**
  - Early diagnosis and treatment of congenital hypothyroidism prevents severe intellectual disability and other neurologic complications.
Hashimoto thyroiditis

4 year old female with thyroid enlargement, fatigue, and daytime somnolence. TSH >150 MIU/L and Free T4 <0.4 NG/DL. Anti-TPO antibodies were very high.
HASHIMOTO or AUTOIMMUNE THYROIDITIS

**Diagnosis**
- Thyroid function test is usually normal
- TSH can be normal, low, or high
- Positive anti-TPO (anti-thyroid peroxidase) and anti-TG (anti-thyroglobulin) antibodies

**Management**
- Follow up labs every 6 months if euthyroid and no symptoms
- If there is evidence of hypothyroidism; levothyroxine can be given
Hashimoto thyroiditis

**Background:**
- Autoimmune destruction of the thyroid
- Family history in 30-40%
- Lymphocytic infiltration

**Clinical:**
- Growth failure, constipation, goiter, dry skin, weight gain, slow recoil of DTR

**Laboratory:**
- High TSH
- Anti-thyroglobulin and anti-peroxidase antibodies

**Therapy:**
- Thyroxine
GRAVES DISEASE

• **Background**
  - Most common cause of hyperthyroidism in pediatrics
  - Immune mediated via thyroid-stimulating immunoglobulins (TSI)
  - TSI These immunoglobulins mimic the action of TSH and stimulate thyroid growth and thyroid hormone overproduction
Hyperthyroidism

**Box 25.8 Clinical features of hyperthyroidism**

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Eye signs (uncommon in children)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety, restlessness</td>
<td>Exophthalmos</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>Ophthalmoplegia</td>
</tr>
<tr>
<td>Sweating</td>
<td>Lid retraction</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Lid lag</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Rapid growth in height</td>
<td></td>
</tr>
<tr>
<td>Advanced bone maturity</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
</tr>
<tr>
<td>Tachycardia, wide pulse pressure</td>
<td></td>
</tr>
<tr>
<td>Warm, vasodilated peripheries</td>
<td></td>
</tr>
<tr>
<td>Goitre (bruit)</td>
<td></td>
</tr>
<tr>
<td>Learning difficulties/behaviour problems</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
</tr>
</tbody>
</table>

25.8 Exophthalmos in Graves disease.
GRAVES DISEASE

- Laboratory
  - Elevated free T4 and T3
  - Suppressed TSH
  - Sometime free T3 is more elevated than T4
  - Anti-thyroid antibodies (TPO) are often present
  - Thyrotropin receptor-stimulating immunoglobulin (TSI) confirm the diagnosis and its absence means remission.
  - Thyroglobulin will be low in exogenous thyroid and high in Graves disease.
GRAVES DISEASE

• Treatment
  – Methimazole is the most common anti-thyroid drug used in US
  
  – Sides effects
    • Transient urticarial rash (the most common side effect)
    • Agranulocytosis (more common in elderly)
    • PTU associated with more cases of liver injuries
GRAVES DISEASE

• Treatment
  – Radioactive iodine
    • Permanent hypothyroidism almost inevitable
  – Beta-blockers to blunt the toxic effect of the circulating T4 and T3.
  – Thyroidectomy if medication not working or not tolerated.

• Treatment follow up
  – Monitor the patient at 6-week to 3-month intervals
    • TFTs (TSH, total T4/free T4 levels), LFTs, and CBC.