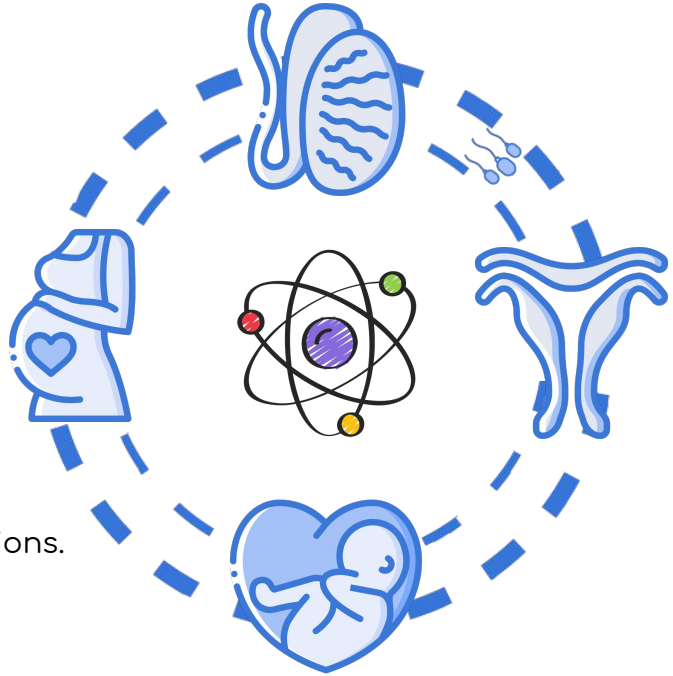
Congenital Adrenal Hyperplasia and Testicular Feminization Syndromes



Objectives:

- Adrenal steroidogenesis.
- Congenital adrenal hyperplasia syndrome:
  - Types, Biochemical characteristics & Clinical manifestations.
- Testicular feminization syndrome.

Color Index:

- Main Topic
- Main content
- Important
- Drs' notes
- Extra info

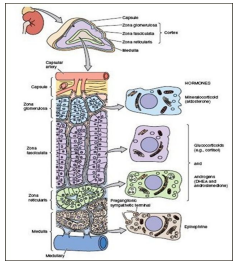
When you find out your normal daily lifestyle is called "quarantine"

Editing File

Introduction

- **Glucocorticoids:**
  - Steroids with cortisol-like activity.
  - Potent metabolic regulators & immunosuppressants.
- **Mineralocorticoids:**
  - Steroids with aldosterone-like activity.
  - Promote renal sodium reabsorption.

Adrenal gland
comprise 3
separate hormone systems:



Zona glomerulosa

- Secretes aldosterone.

Zona fasciculata & reticularis:

- Secrete cortisol & the adrenal androgens.

Adrenal medulla

- Secretes catecholamines (mainly epinephrine).

Hermaphroditism or Intersex

★ **Definition:** A person who has neither standard male or standard female anatomy. Discrepancy between the type of gonads and the external genitalia.

★ **Types:**

1. **True hermaphrodite** (individual is born with both ovary and testicles).
2. **Female PseudoHermaphrodite**[1] (FPH, only ovary).
3. **Male PseudoHermaphrodite**[2] (MPH, only testis).

1- 46,XX: Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (eg, congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).

2- 46,XY: Testis present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).

Steroidogenesis and Congenital Adrenal Hyperplasia Syndrome

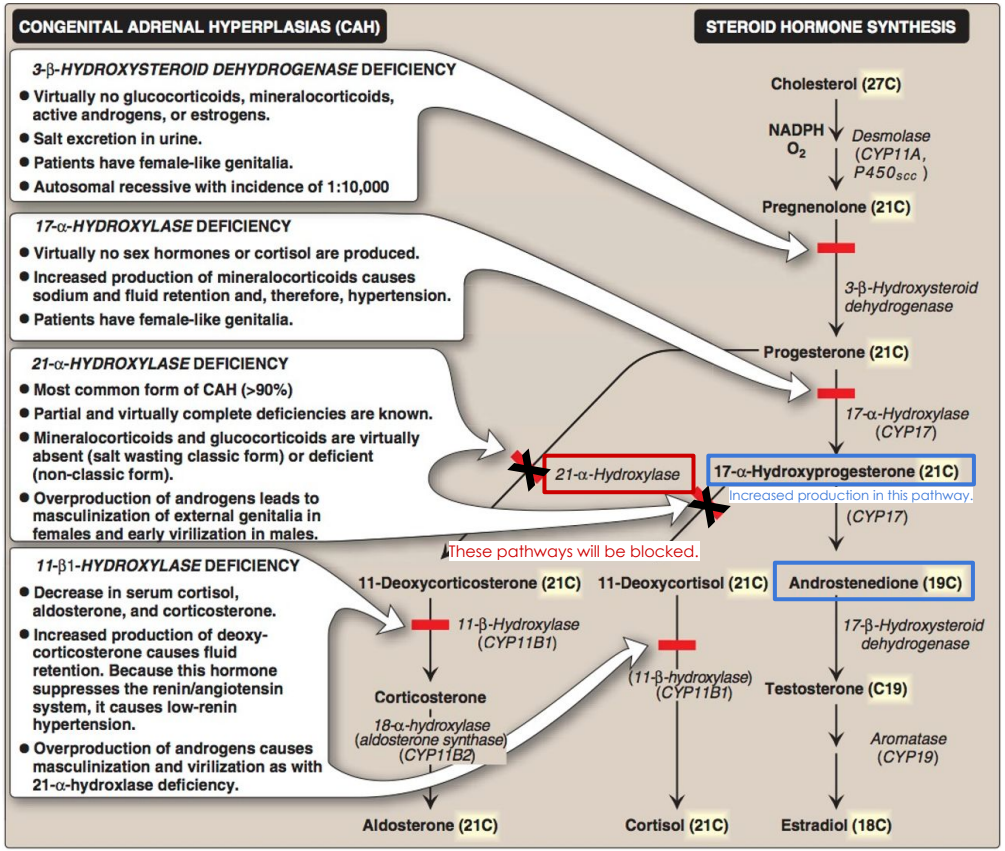
Congenital Adrenal Hyperplasia (CAH) Syndromes:

- It is the result of an inherited enzyme defect in steroid biosynthesis.
- **The adrenals :**
  - **Cannot secrete cortisol** → absent negative feedback to the pituitary → ACTH continues to drive steroid biosynthesis → **adrenal hyperplasia and accumulation of cortisol precursors** (depending on which enzyme is lacking).
  - **Cannot secrete aldosterone** → electrolyte disturbances:
    - **Hyponatremia**
    - **Hyperkalemia**
- The condition might be fatal unless diagnosed early.

Types of CAH syndromes: Arranged from most common to least common.

1. **21 α-Hydroxylase deficiency.**
2. **11 β-Hydroxylase deficiency.**
3. **17 α-Hydroxylase deficiency.**
4. **3 β-Hydroxysteroid dehydrogenase deficiency.**

All syndromes are required (This figure is important).



21 α-Hydroxylase Deficiency

General info

- The **most common** type of CAH **(90%)**.
- **Autosomal recessive** condition.

Pathogenesis

- Impaired synthesis of both cortisol & aldosterone, steroidogenesis is predominantly shunted toward sex steroid production (which does not require 21 -hydroxylase).
- ↓ cortisol → ↑ ACTH secretion (Lack of negative feedback) → Bilateral Adrenal gland hyperplasia.
- **Accumulated 17-α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones → signs of androgen excess:** due to the action of androgens on peripheral tissue.
  - Ambiguous genitalia in newborn girls (FPH).
  - Rapid postnatal growth in both sexes.
- **Severe cases: mineralocorticoid deficiency** → salt & H_2O loss → hypovolemia & **shock** → **neonatal adrenal crisis**

Note: Late presentation (adult life) is possible in less severe cases.

Clinical pictures

1) **Complete enzyme defect** → ↑ stimulation of adrenal androgen production → **virilization** in **baby girls** & **precocious puberty** in **boys**.
2) **Partial enzyme defect** → **late onset** form → **menstrual irregularity** & **hirsutism** **in young females**.

Genetics

Mutations in the CYP21 gene:

- Deletions, Nonsense, Missense.

DNA testing of CYP21:

- **For prenatal diagnosis** and confirmation of diagnosis.

Diagnosis

- Serum sample taken **at least 2 days after birth** (earlier samples may contain maternally derived 17-D-hydroxyprogesterone):
  - ↑ plasma [17-α-hydroxyprogesterone] as early as 4 days after birth.

1) **Classic (complete) deficiency:** is characterized by **markedly elevated serum levels of 17-α-hydroxyprogesterone**
2) **Late-onset (partial) deficiency:** may **require corticotropin (ACTH) stimulation test:**
   - **Measure base-line and stimulated levels of 17-α- hydroxyprogesterone.**
   - **High level of 17-α-hydroxyprogesterone after stimulation is diagnostic.**

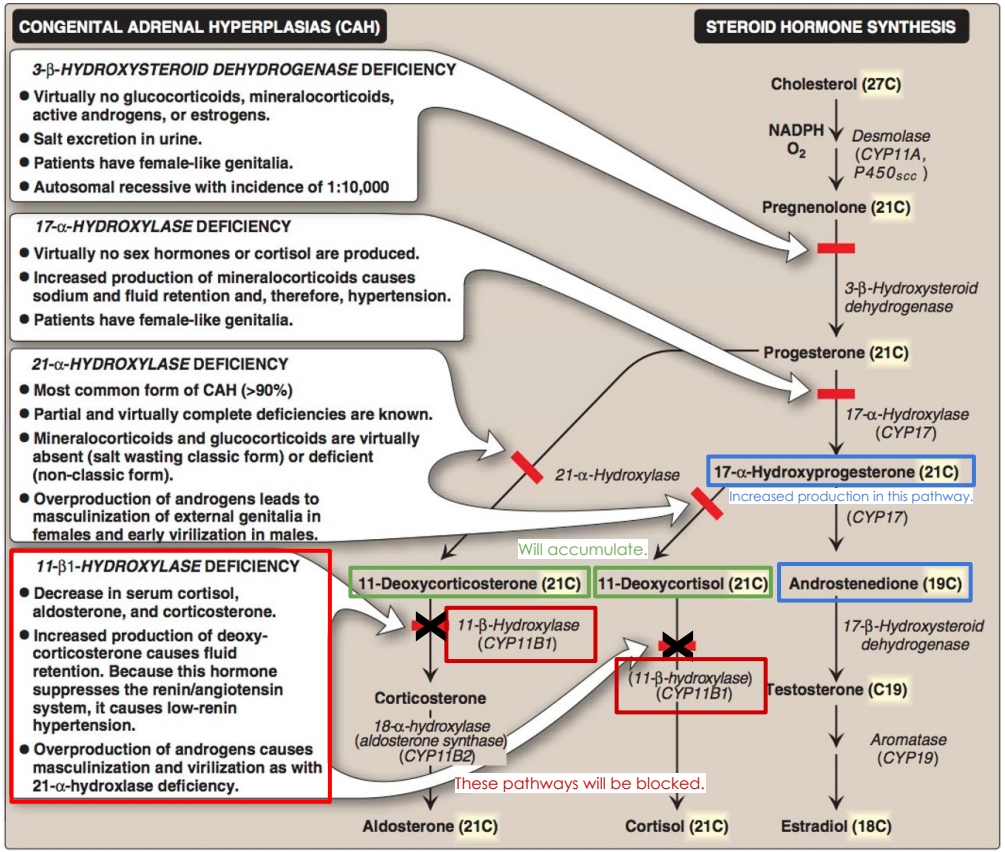
overview

11 B-Hydroxylase Deficiency

- It is the result of an inherited **enzyme defect** in steroid biosynthesis.
- Leads to high concentrations of 11-deoxycortisol.
- **Leads to high levels of 11-deoxycorticosterone with mineralocorticoid effect (salt and water retention).**
- Suppresses renin/angiotensin system → **low-renin hypertension.**
- **Masculinization** and **Precocious sexual development in females** (FPH) and **early virilization in males.**

11-deoxycorticosterone has the same activity as aldosterone → salt and water retention → hypertension.

Imp to know it is low renin hypertension, because renin system is activated when we have hypotension but here it is not related to hypotension or hypovolemia it is genetic disease.



Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

Disorders of Male Sexual Differentiation

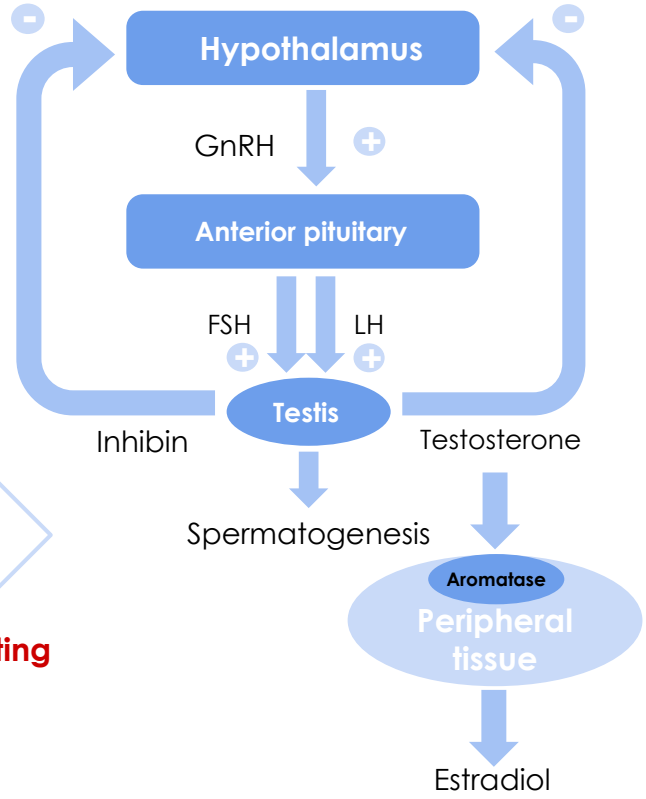
- They are **rare** group of disorders.
- **The defect may be in:**
  - **Androgen receptors** (inactive androgen receptors in target tissues cannot respond to stimulation by circulating testosterone ; e.g., **Testicular feminization syndrome**).

Testicular Feminization Syndrome

- **46, XY karyotype** (Normal Male).
- X-linked recessive disorder.

Androgen receptor resistance. → high testosterone blood level. → In **peripheral tissue**, **testosterone** will be **converted by aromatase into estradiol.** → **Feminization.**

Patients have **normal testes** & **produce normal amounts of müllerian-inhibiting factor (MIF)**[1], therefore, affected individuals **do not have** fallopian tubes, a uterus, or a proximal (upper) vagina.



1- Sertoli cells secrete Müllerian inhibitory factor (MIF also known as, antimullerian hormone) that suppresses development of paramesonephric ducts.

Testicular Feminization Syndrome (Androgen Insensitivity Syndrome)

Clinical picture

Complete androgen insensitivity syndrome (CAIS).

female external genitalia with normal labia, clitoris, and vaginal introitus (MPH).

Partial androgen insensitivity syndrome (PAIS).

mildly virilized female external genitalia (clitorimegaly without other external anomalies) to **mildly undervirilized male external genitalia** (hypospadias and/or diminished penile size.

Laboratory diagnosis

Increased (or normal) testosterone and dihydrotestosterone blood levels.

Fluorescent in situ hybridization (FISH): Presence of a Y chromosome can be confirmed by probes for the SRY region of the Y chromosome. These offer a much quicker turnaround time than conventional karyotypes.

Karyotype: differentiate an under-masculinized male from a masculinized female.

DNA tests and mutation analysis for androgen receptor gene: Complete or partial gene deletions, point mutations, or small insertions deletions.

Imaging Studies "Pelvic ultrasound": Absence of fallopian tubes and uterus.

Summary

<table>
<tr><td rowspan="2">CAH</td><td>21 α-Hydroxylase deficiency</td><td>
General info:
• The most common type of CAH (90%).
• Autosomal recessive condition.
Pathogenesis:
• Accumulated 17-α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones → signs of androgen excess: due to the action of androgens (17-α-hydroxyprogesterone, Androstenedione) on peripheral tissue.
  ○ Ambiguous genitalia in newborn girls (FPH)
  ○ Rapid postnatal growth in both sexes
• Severe cases: mineralocorticoid deficiency → salt & H2O loss → hypovolemia & shock → neonatal adrenal crisis
Clinically:
• Complete enzyme defect → stimulation of adrenal androgen production → virilization in baby girls & precocious puberty in boys.
• Partial enzyme defect → late onset form → menstrual irregularity & hirsutism in young females.
Diagnosis:
• Serum sample taken at least 2 days after birth (earlier samples may contain maternally derived 17-D-hydroxyprogesterone)
• Classic (complete) deficiency is characterized by markedly elevated serum levels of 17-D-hydroxyprogesterone
• Late-onset (partial) deficiency may require corticotropin (ACTH) stimulation test:
  ○ Measure base-line and stimulated levels of 17-α- hydroxyprogesterone.
  ○ High level of 17-α-hydroxyprogesterone after stimulation is diagnostic
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<tr><td>11 β-Hydroxylase deficiency</td><td>
• Leads to high concentrations of 11-deoxycortisol
• Leads to high levels of 11-deoxycorticosterone with mineralocorticoid effect (salt and water retention)
• Suppresses renin/angiotensin system low-renin hypertension
• Masculinization in females (FPH) and early virilization in males
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<tr><td colspan="2">Testicular Feminization Syndrome</td><td>
General info:
• 46, XY karyotype, X-linked recessive disorder
• Androgen receptor resistance → high testosterone blood level
• In peripheral tissue, testosterone will be converted by aromatase into estradiol → feminization
• Patients have normal testes & produce normal amounts of müllerian-inhibiting factor (MIF), therefore, affected individuals do not have fallopian tubes, a uterus, or a proximal (upper) vagina.
Clinical pictures:
• Complete androgen insensitivity syndrome (CAIS): female external genitalia with normal labia, clitoris, and vaginal introitus (MPH)
• Partial androgen insensitivity syndrome (PAIS): mildly virilized female external genitalia (clitorimegaly without other external anomalies) to mildly undervirilized male external genitalia (hypospadias and/or diminished penile size)
Diagnosis:
• Karyotype: differentiate an under masculinized male from a masculinized female.
• Fluorescent in situ hybridization (FISH): Presence of a Y chromosome can be confirmed by probes for the SRY region of the Y chromosome. These offer a much quicker turnaround time than conventional karyotypes.
• Increased (or normal) testosterone and dihydrotestosterone blood Levels
• DNA tests and mutation analysis for androgen receptor gene: Complete or partial gene deletions, point mutations, or small insertions/deletions
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Quiz

MCQs :

Q1: Which of the following enzyme deficiencies will lead to absence of glucocorticoids , mineralocorticoid and androgens?

a) 21-a-hydroxylase **b)** 17-a-hydroxylase **c)** 11-B-hydroxylase **d)** 3-B-HSD

Q2: 21-a-hydroxylase enzyme deficiency leads to an increase in which one of the following?

a) Aldosterone **b)** 17-a-hydroxyprogesterone
c) 11-Deoxycorticosterone **d)** Cortisol

Q3: In which type of enzyme deficiency does virilization in baby girls & precocious puberty in boys occur?

a) Partial 21-a-Hydroxylase Deficiency **b)** 11a-Hydroxylase Deficiency
c) complete 21-a-Hydroxylase Deficiency **d)** 17-a-Hydroxylase Deficiency

Q4: Testicular feminization syndrome is …….. disorder.

a) Autosomal recessive **b)** Autosomal dominant **c)** X-linked recessive **d)** X-linked dominant

Q5: Which one of the following investigation results are consistent with the diagnosis of complete androgen insensitivity syndrome (CAIS)?

a) Absence of SRY gene by FISH **b)** High testosterone blood level
c) XX karyotype **d)** Identification of uterus and fallopian tubes by pelvic ultrasound

SAQs :

Q1: What are the three types of Hermaphroditism?

Q2: Name 4 types of CAH Syndromes

Q3: Where is the defect in Testicular feminization syndrome?

Q4: How can we diagnose Testicular feminization syndrome?

★ **MCQs Answer key:**

1) D 2) B 3) C 4) C 5) B

★ **SAQs Answer key:**

1) 1- True hermaphrodite
2- Female pseudohermaphrodite
3- Male pseudohermaphrodite

2) 1- 21-a-Hydroxylase deficiency
2- 11-B-Hydroxylase deficiency
3- 17-a-Hydroxylase deficiency
4- 3-B-Hydroxysteroid dehydrogenase deficiency

3) In androgen receptors either complete mutation or partial.

4) Karyotype, FISH, dihydrotestosterone blood levels, mutation analysis and Pelvic ultrasound.

Team members

Girls Team:

- Ajeed Al-Rashoud
- Nouf Alhumaidhi
- Noura Alturki

Boys Team:

Mashal Abaalkhail
Naif Alsolais
Mohammed Alhumud

Team Leaders

Lina Alosaimi

Mohannad Alqarni

Take care 💜

438 BIOCHEMISTRY TEAM

We hear you