"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Congenital Adrenal Hyperplasia and Testicular Feminization Syndromes

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Reproductive block

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Objectives:

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

You should know **All** CAH Syndromes:
- 21-Hydroxylase deficiency
- 11-Hydroxylase deficiency
- 17-Hydroxylase deficiency
- 3-Hydroxysteroid dehydrogenase deficiency

The last two syndromes are not found in doctor's slide. However, they're include in our objectives! You can find them in Steroidogenesis diagram (slide 11), or in the summary below (slide 15)

Adrenal Glands

The adrenal glands comprise 3 separate hormone systems:

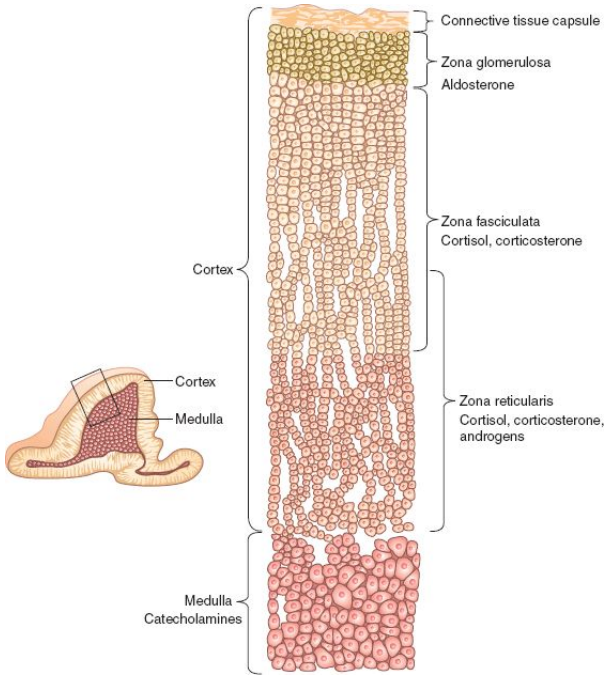
1. Zona glomerulosa: Secretes aldosterone.
2. Zona fasciculata & reticularis: Secrete cortisol & the adrenal androgens.
3. Adrenal medulla: Secretes catecholamines (mainly epinephrine).

Glucocorticoids:

Steroids with cortisol-like activity.
Potent metabolic regulators & immunosuppressants.

Mineralocorticoids:

Steroids with aldosterone-like activity.
Promote renal sodium reabsorption.



IMPORTANT!

Hermaphroditism or Intersex

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

- True hermaphrodite (ovary plus testis).
- Female pseudohermaphrodite (FPH, only ovary).
  - She's an (XX) female with ovaries, and pseudohermaphrodite is bc she has male external genitalia
- Male pseudohermaphrodite (MPH, only testis).
  - He's an (XY) male with testis, and pseudohermaphrodite is bc he has female external genitalia

A pseudohermaphrodite is a person whose gonads are consistent with the chromosomal sex but who has external genitalia of the opposite sex

The picture is important and very very useful!

Overview

شرحنا لكم ال ***Pathway+CAH***
شيكو عليه ب***Drive***

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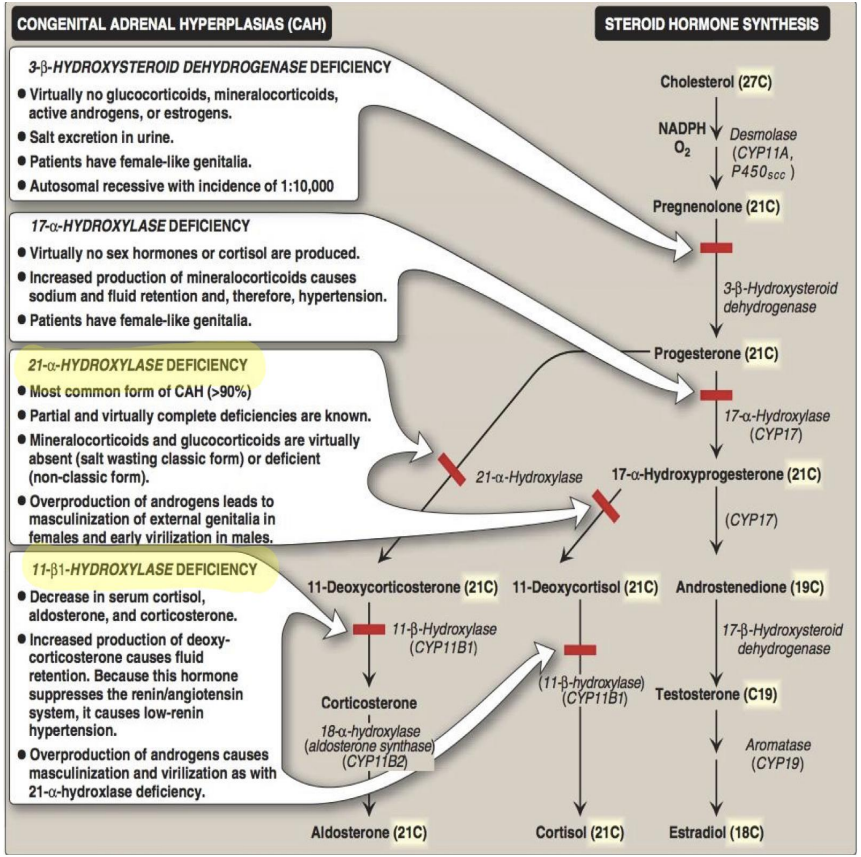

- The steroid hormone pathway *"seen on the left"* is a multistep pathway that requires multiple enzymes.
- If one of the enzymes is deficient, the pathway gets blocked.
- The precursors accumulate and maybe shunted towards another pathway, and the results are deficient *"the red lines refer to enzyme deficiencies".*
- In this lecture, we will focus on 2 enzymes, 21α-Hydroxylase and 11β-Hydroxylase deficiency.
- Notice that cortisol is one of the final results of this pathway, meaning if any enzyme deficiency happens, cortisol will not be formed, and since cortisol is the only steroid hormone here that has a negative feedback on ACTH, ACTH is always very high.
- Since ACTH is high, the adrenals are always hyperplastic.

Steroidogenesis and Congenital Adrenal Hyperplasia

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Congenital Adrenal Hyperplasia:

It is the result of an inherited enzyme defect in steroid biosynthesis.

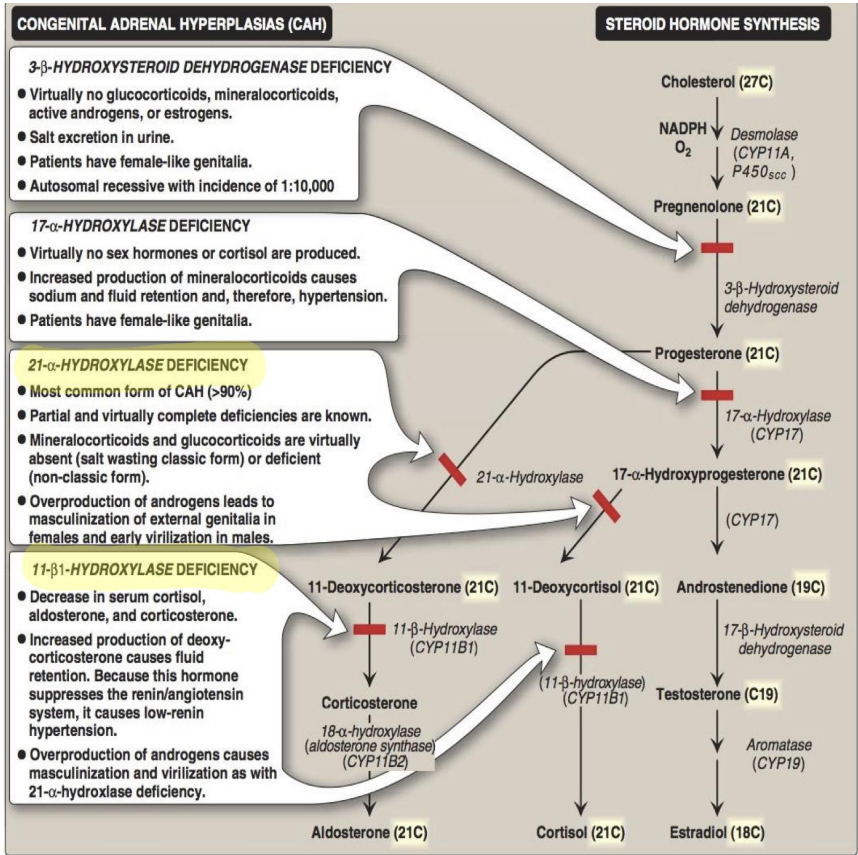
The Adrenals

You don't have to memorize the genes in this lecture

- 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: 1- Hyponatremia, 2- Hyperkalemia → The condition might be fatal unless diagnosed early

Steroidogenesis



CAH Syndromes

The enzyme defect arrange according the most common to less common :

- 21α-Hydroxylase deficiency
- 11β-Hydroxylase deficiency
- 17α-Hydroxylase deficiency
- 3β-Hydroxysteroid dehydrogenase deficiency

21α -Hydroxylase Deficiency

The **most common** type of CAH (90%)

Clinically: has 2 pictures

Complete enzyme defect
Increase stimulation of adrenal androgen production → virilization in baby girls & precocious puberty in boys.

-Mutations happen in the active site.
-These symptoms because all of 17-hydroxyprogesterone is converted to testosterone

Partial enzyme defect
late onset form → menstrual irregularity & hirsutism in young females.

- Males are not affected by Partial enzyme defect.
- Mutations happen in a place other than the active site.

Laboratory diagnosis:

Increase plasma [17-hydroxyprogesterone] as early as 4 days after birth

Clinical findings: (important)

- Low cortisol and aldosterone
- Hypotension
- Hyponatremia and hyperkalemia
- High 17-a-hydroxyprogesterone
- High testosterone

21α- Hydroxylase Deficiency

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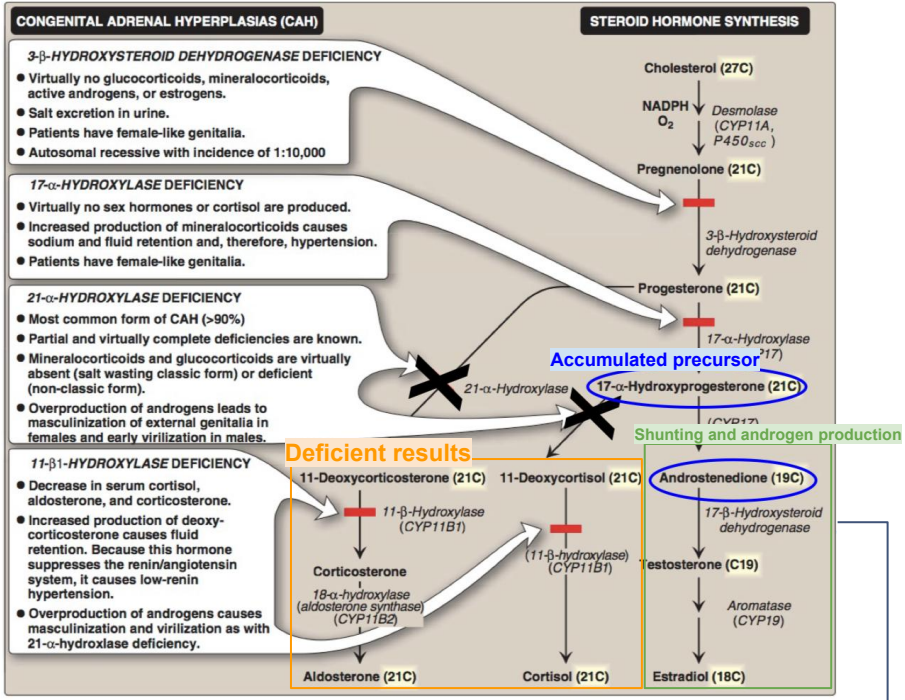
- Autosomal recessive condition
- Impaired synthesis of both cortisol & aldosterone
- ↓[cortisol] → ↑ ACTH secretion → Adrenal gland hyperplasia
- Accumulated 17-a-hydroxyprogesterone are diverted to the biosynthesis of sex hormones → signs of androgen excess:
- Ambiguous genitalia in newborn girls (FPH)
- Rapid postnatal growth in both sexes
- Severe cases: mineralocorticoid deficiency salt & H_2O loss → hypovolemia & shock → neonatal adrenal crisis
- Late presentation (adult life) is possible in less severe cases



In peripheral tissues

Virilization of female

Precocious sexual development in males

21α-Hydroxylase Deficiency: **Genetics**

You don't have to memorize the gene mutations and what they mean

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Mutations in the CYP21 gene:
Deletions, Nonsense, Missense

DNA testing:
For prenatal diagnosis and confirmation of diagnosis

Leading to wrong protein → wrong enzyme →enzyme deficiency

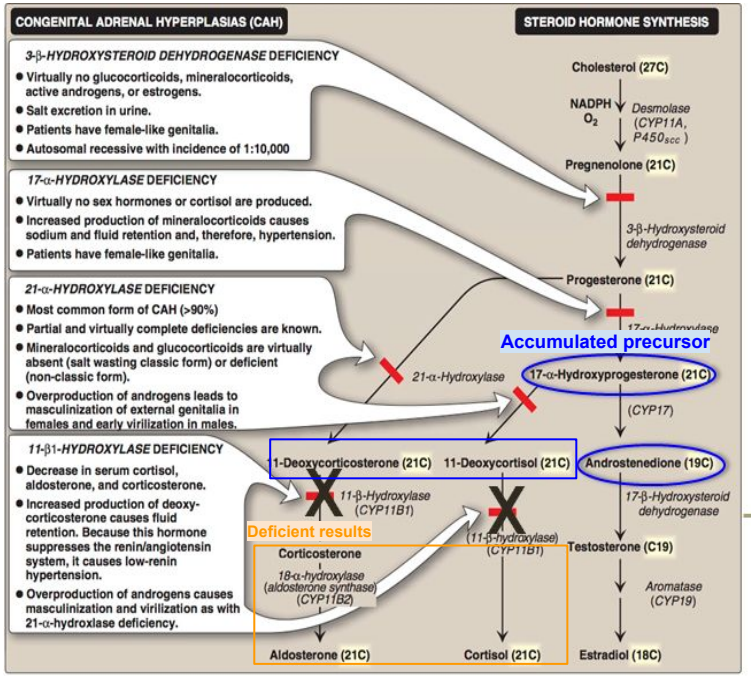
21α-Hydroxylase Deficiency: **Diagnosis**

- Serum sample taken at least 2 days after birth (earlier samples may contain maternally derived 17-a-hydroxyprogesterone).
- Classic (complete) deficiency is characterized by markedly elevated serum levels of 17-a-hydroxyprogesterone.
- Confirmation is by CYP21 gene
- Late-onset (partial) deficiency (borderline) may require corticotropin (ACTH) stimulation test:
  - Measure baseline and stimulated levels of 17-a-hydroxyprogesterone
  - High level of 17-a-hydroxyprogesterone after stimulation is diagnostic

When we test the baby's 17-a-hydroxyprogesterone and its neither high nor normal (borderline) we need to confirm the diagnosis just like in addison disease where we will give ACTH. Increase in 17-a-hydroxyprogesterone means that there's blockage in the pathway which will confirm CAH

11β-Hydroxylase Deficiency

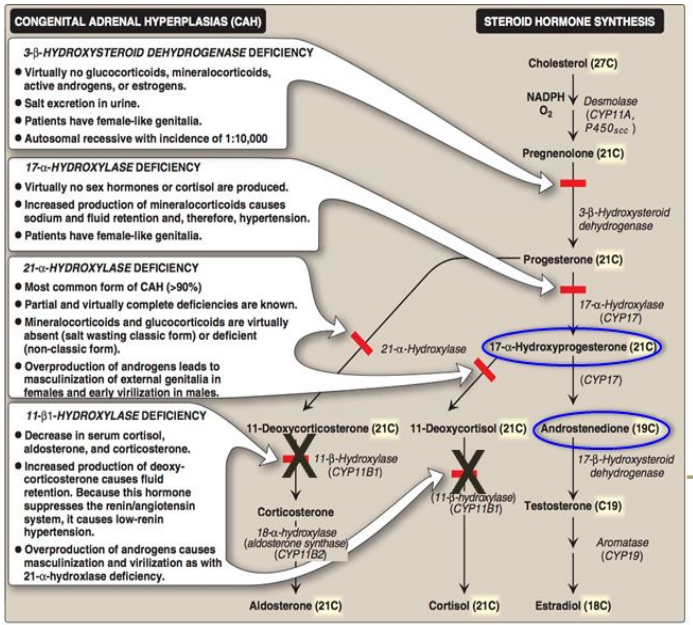
- Leads to high concentrations of 11-deoxycortisol and 11-deoxycorticosterone
- 11-deoxycorticosterone has mineralocorticoid effect (salt and water retention+hypertension)
- Suppresses renin/angiotensin system → low-renin hypertension
- Masculinization in females (FPH) and early virilization in males (same as 21 hydroxylase deficiency)



- Deficiency in this enzyme is less common.
- It is similar to 21-Hydroxylase Deficiency that (aldosterone \ cortisol and) are deficient whereas testerone and 17-a hydroxyprogesterone is excess.
- 11-deoxycortisol and 11-deoxycorticosterone are also accumulated.
- 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.

In peripheral tissues → Virilization of ♀
In peripheral tissues → Precocious sexual development in ♂

Read it and know about it but focus on the first 2 enzymes



3B-hydroxysteroid dehydrogenase deficiency:

- Virtually no glucocorticoid, mineralocorticoid, active androgens, or estrogens.
- Salt excretion in urine (no absorption of Na).
- Patient have female-like genitalia.
- Autosomal recessive with incidence of 1:10,000.

17-a-hydroxylase deficiency:

- Virtually no sex hormones or cortisol are produced.
- Increased production of mineralocorticoids causes sodium and fluid retention and, therefore, hypertension.
- Patients have female-like genitalia.

Testicular Feminization Syndrome
(Androgen Insensitivity Syndrome)

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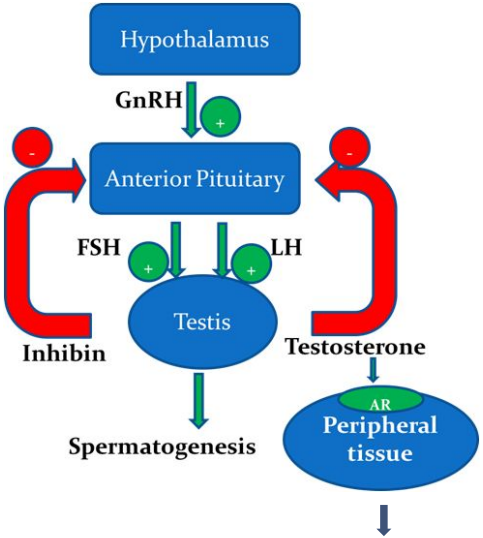
Disorders of Male Sexual Differentiation

- They are **rare** group of disorders
- The defect may be in:
  - Androgen receptors (inactive androgen receptors → target tissues cannot respond to stimulation by circulating testosterone; e.g., Testicular feminization syndrome)[1]

Testicular Feminization Syndrome

- 46, XY karyotype (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)[2], therefore, affected individuals do not have fallopian tubes, a uterus, or a proximal (upper) vagina.



Erastidol
(Testosterone is converted to Erastidol in peripheral tissue by Aromatase enzyme), hence although patient has testes but he has a lot of estrogen in his body

1. Testes are healthy and producing normal amount of testosterone but Androgen receptor is inactive because it is a protein so any mutation will cause it not to accept testosterone, so the patient has a lot of testosterone but the cells can not utilize it.
2. Müllerian inhibiting factor is produced from the testis , it inhibit formation of female external genitalia.

Clinical Picture

- **Complete androgen insensitivity syndrome (CAIS)*:** female external genitalia with normal labia, clitoris, and vaginal introitus (MPH) (male pseudohermaphrodite).
- **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) (between male and female).

Laboratory 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.

Further Investigations

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

*Mutation on the receptor completely damages the receptor, no testosterone is going inside the cell. All features of external genitalia only is like female but he has testis. Do not have fallopian tubes, a uterus, or a proximal (upper) vagina because of the effect of MIF

A) Congenital adrenal hyperplasia: we have 4 enzymes deficiency:

- **21-Hydroxylase deficiency (Imp):**
  - low cortisol, low aldosterone, high testosterone, high 17-a-hydroxyprogesterone, hypotension, hyponatremia, hyperkalemia, autosomal recessive.
  - confirmation by gene detection.
  - clinical: early puberty and ambiguous genitalia in female if late onset hairstumsim.

- **11-Hydroxylase deficiency(imp):**
  low cortisol, low aldosterone, high 11-deoxycorticosterone, hypertension.

- **17-Hydroxylase deficiency**

- **3-Hydroxysteroid dehydrogenase deficiency**

B) Testicular Feminization Syndrome:

- High Testosterone, problem is inactive androgen receptor, FISH is used to detect Y chromosome, Patient is XY (male).
- It can either be partial or complete:
  In complete (external genitalia is like female), affected individuals do not have fallopian tubes, a uterus, or a proximal (upper) vagina because of MIF secreted from healthy testis.

Summary

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Congenital Adrenal Hyperplasia (CAH) Syndromes : It is the result of an inherited enzyme defect in steroid biosynthesis

21 α-Hydroxylase deficiency :

• The most common type of CAH (90%)
• Mutations in the CYP21 gene
• There is low or absent mineralocorticoids and glucocorticoids and high androgens
• Laboratory diagnosis: ↑ plasma [17-α-hydroxyprogesterone] as early as 4 days after birth
• Clinical diagnosis :
-Ambiguous genitalia in newborn girls (FPH)
-Rapid postnatal growth in both sexes
-In Severe cases ⟶ neonatal adrenal crisis
• Diagnosis :
-Serum sample taken at least 2 days after birth
-Classic (complete) deficiency is characterized by markedly elevated serum levels of 17-α-hydroxyprogesterone
-Late-onset (partial) deficiency may require corticotropin (ACTH) stimulation test.

11 β-Hydroxylase deficiency :

•leads to high concentrations of 11-deoxycortisol and 11-deoxycorticosterone
•Suppresses renin/angiotensin system ⟶ low-renin hypertension
•Masculinization in females (FPH) and early virilization in males

17 α-Hydroxylase deficiency :

•High mineralocorticoids
•Patient have female like genitalia

3 β-Hydroxysteroid dehydrogenase deficiency :

•no mineralocorticoids, glucocorticoids and androgens
•Patient have female like genitalia

Testicular Feminization Syndrome (Androgen Insensitivity Syndrome) :

- The defect may be in Androgen receptors
- X-linked recessive disorder
- Androgen receptor resistance ⟶ high testosterone blood level which will be converted by aromatase into estradiol ⟶ feminization
- Patients have normal testes, and do not have fallopian tubes, a uterus, or a proximal (upper) vagina.

Laboratory Diagnosis :

- Karyotype: differentiate an undermasculinized male from a masculinized female.
- (FISH): Presence of a Y chromosome can be confirmed by probes for the SRY region (it is much quicker)
- Increased (or normal) testosterone and dihydrotestosterone blood levels
- DNA tests and mutation analysis for androgen receptor gene
- Pelvic ultrasound

MCQs:

1- Which of the following enzyme deficiency is most common in CAH?
A- 11-hydroxylase
B- 21b-hydroxylase
C- 17- hydroxylase
D- 21a-hydroxylase

2- CAH with accumulation of 17a- hydroxyprogesterone is an indication of deficiency in which enzyme?
A- 17-hydroxylase
B- 3 b- hydroxylase
C- 21 b- hydroxylase
D- 21 a- hydroxylase

3- Which of the following is a late complication of partial 21 alpha hydroxylase deficiency ?
A- Virilization baby girls
B- Precocious puberty in boys
C- Gigantism
D- Hirsutism

4- Which of the following explains testicular feminization syndrome?
A- Androgen receptors resistance
B- Deficiency of hormones
C- Hypothalamus pituitary axis defect
D- X-linked dominant disorder

5- Which of the following will be low in case of 21 alpha hydroxylase?
A- Androstenedione
B- Progesterone
C- Aldosterone
D- estrogen

1- D
2- D
3- D
4- A
5- C

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Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- طارق العميم
- حسام الرويتع
- عبدالملك الشرهان
- انس القحطاني
- صالح الوكيل
- سلطان الناصر
- معن شكر
- محمد الصويغ
- نايف المطيري

Girls team

- لجين عبدالله
- العنود المنصور
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