In the Name of God

# Non-classical Congenital Adrenal Hyperplasia (NCCAH)

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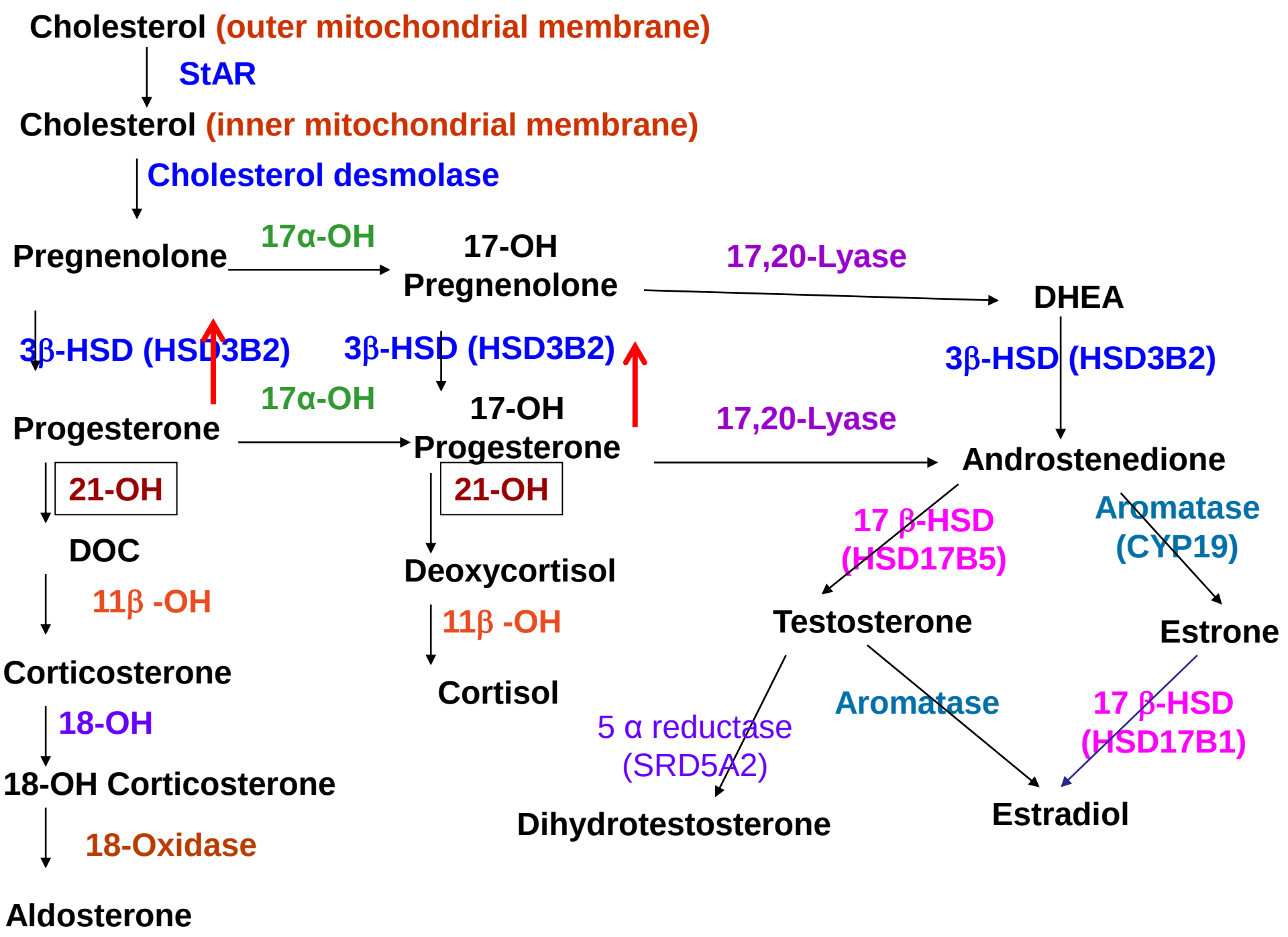
# Definition

Congenital adrenal hyperplasia (CAH)

describes a group of inherited autosomal recessive disorders characterized by enzymatic defect in cortisol biosynthesis


Cholesterol (outer mitochondrial membrane)
StAR
Cholesterol (inner mitochondrial membrane)
Cholesterol desmolase
Pregnenolone
17α-OH
17-OH Pregnenolone
17,20-Lyase
DHEA
3β-HSD (HSD3B2)
3β-HSD (HSD3B2)
3β-HSD (HSD3B2)
Progesterone
17α-OH
17-OH Progesterone
17,20-Lyase
Androstenedione
21-OH
21-OH
DOC
Deoxycortisol
17 β-HSD (HSD17B5)
Aromatase (CYP19)
11β -OH
11β -OH
Testosterone
Estrone
Corticosterone
Cortisol
18-OH
Aromatase
17 β-HSD (HSD17B1)
5 α reductase (SRD5A2)
18-OH Corticosterone
Dihydrotestosterone
Estradiol
18-Oxidase
Aldosterone

# 21-hydroxylase deficiency (21-OHD)

- Is reported > 95% of the cases of CAH

It is one of the most common known autosomal recessive disorders

- It is divided to
  - Classical
  - Nonclassical
- Classical
  - Salt wasting (SW)
  - Simple virilizing (SV)

# Incidence rate of Non-classical congenital adrenal hyperplasia (NCCAH)

It is a common monogenic inherited disease

- Caucasians (1:1000)
- Ashkenazi Jews (1:27)
- Hispanics (1:53)
- Yugoslavs (1:62)
- Italians (1:300)

# Non-classical congenital adrenal hyperplasia (NCCAH)

- It lacks genital ambiguity and salt wasting
- Is not immediately lifethreatening at birth
- Many remain asymptomatic during childhood and adolescence
- Present later in life
- Misdiagnosed as other hyperandrogenic disorders

# Pathophysiology of NCCAH

There is no evidence of ACTH or CRH excess

- Progesterone and 17-OHP are increased → disruption of the hypothalamic-pituitary-ovarian axis
- Impaired hypothalamic sensitivity to progesterone
- Rapid GnRH pulse
- LH hypersecretion
- Excessive ovarian androgen secretion

# Precocious Puberty

- It is hypothesized that in some cases, the peripheral aromatization of adrenal androgens to estrogens may activate the hypothalamic-pituitary-gonadal axis, leading to secondary precocious puberty

# Clinical picture of NCCAH in childhood

- Premature pubarche is the first sign in 92% of the cases
- The earliest case that was reported had 6 months of age, but it is usually seen from 5 yr of age or later)
- Perianal hair
- Apocrine odor

# Clinical picture of NCCAH in childhood

- Advanced bone age
  - Tall stature in childhood
- As a consequence of rapid epiphyseal fusion
  - Short stature in adulthood
  - Truncated final height

# Rare Clinical picture of NCCAH in childhood

- Clitoral enlargement
- labial adhesion
- Phallic enlargement with prepubertal testes
- Hoarseness of voice

## Uncommon presenting features

- Peripubertal gynecomastia
- Adrenocortical incidentaloma

# Adolescent & Adult Manifestations

- Hyperandrogenic signs resembling polycystic ovary syndrome (63%)
- Hirsutism (the most common 59%, 78%)
- Acne (33%)
- Androgenic Alopecia

# Adolescent & Adult Manifestations

- Menstrual dysfunction,
  - Oligomenorrhea (54%)
  - Primary (9%) or Secondary amenorrhea
- Anovulation or decreased fertility (12%)
- May have normal reproductive function

# Adolescent & Adult Manifestations

- Many adult patients remain asymptomatic (more in males)
- Become aware because:
  - Diagnosis of another family member and consequent testing

# According to 2003 consensus statement Diagnostic criteria of Polycystic ovary syndrome (PCOS) are Presence of two of the three findings

- 1) Polycystic ovaries by sonography
- 2) Clinical or biochemical evidence of androgen excess
- 3) Chronic menstrual abnormalities or anovulation
- In addition to exclusion of other known disorders
- NCCAH also presents with hyperandrogenemia and anovulation, and thus should be ruled out in patients with PCOS

# According to NIH 56% and Rotterdam 72.8% of NCCAH fulfilled the PCOS criteria but

- Are younger
- More hirsute
- Have significantly higher levels of
  - Testosterone
  - Free testosterone
  - 17 OHP

Ovarian ultrasound display

- 77% polycystic ovaries
- 41% increased ovarian size

# NCCAH, Genetic study

- Mild mutations on both alleles or one severe and one mild mutation of *CYP21A2* (compound heterozygote)
- Half of the cases may be heterzygote carriers of CYP21A2 mutation
- Missense mutations in exon 7 (V281L) and exon 1 (P30L), reduce enzymatic activity in cultured cells to 20–50% of normal
- Missense mutations in exon 8 (R339H) and exon 10 (P453S) are associated with the nonclassical phenotype

# Enzymatic Function in CAH

- Classic → 0 – 5%
- NCCAH → 50 – 80 %

# Laboratory tests for NCCAH

Clinical guidelines by the Endocrine Society recommend

- Baseline non-stimulated value of 17 OHP is the screening tool for NCCAH
- 17 OHP level is extremely high in the luteal phase in half of healthy females
- 17 OHP should be measured in follicular phase in adult females

# Laboratory tests for NCCAH

- Unstimulated 17- OHP 07:30 – 08:00 hr in the preovulatory (follicular phase) between 5.1 nmol/L (1.7 ng/ml) and 9 nmol/L (3 ng/ml) is sufficient for the diagnosis

- 8:00 AM 17 OHP levels >6 nmol/L (2 ng/ml) in the follicular phase in menstruating females capture 90% of NCCAH

- It had 100% sensitivity & 99% specificity for the detection of NCCAH in one cohort

# Diagnosis

In a study

Basal 17-OHP > 2 ng/mL was seen in

- 25% lean women with PCOS
- 20% obese women with PCOS
- 7% control women

I.B. Armengaud, et.al, J.C EM 94, 2835 – 2840 , 2009

# Diagnosis

- A level of basal 17 OHP of 4.6 nmol/L (1.5 ng/ml) was suggested as a threshold for ACTH testing

ACTH Test

- Synacthen test, ACTH (Cortrosyn, 0.25 mg IV)
- Blood sampling (0 , 30, 60 min) →

**17 OHP 10 – 15 ng/mL is diagnostic**

# Techniques used for 17 OHP evaluation

- 17 OHP levels are measured by a variety of immunoassay methods
- The most accurate and reliable results were achieved by the implementation of the combination of liquid chromatography with mass spectrometry (LC-MS/MS)
- But LC-MS/MS is not universally used

# LC-MS/MS

- Many false positive 17 OHP measurements were found when LC-MS/MS measurements were compared with standard methods due to lower thresholds
- LC-MS/MS, is less prone to cross-reactivity and interferences
- The screening and diagnostic thresholds for 17 OHP by LC-MS/MS are necessary to be defined

# Diagnosis

In equivocal cases a complete steroid profile should be performed after the ACTH stimulation test to differentiate 21-hydroxylase deficiency from other enzyme defects and establish a firm diagnosis

- Cortisol
- 17 OHP
- Dehydroepiandrosterone
- Androstenedione
- 11-deoxycorticosterone
- 11-deoxycortisol
- 17-OH-pregnenolone

# NCCAH MANAGEMENT FROM THE FIRST MANIFESTATION TO THE ADULT LIFE

- The first question to be addressed is whether glucocorticoid (GC) therapy is indicated?
  - By providing sufficient cortisol concentrations to the patient, CRH-ACTH axis stimulation will be tapered, leading to decreased adrenal androgen production
  - Hydrocortisone treatment is indicated if Inadequate cortisol response post ACTH stimulation is existed

# NCCAH MANAGEMENT FROM THE FIRST MANIFESTATION TO THE ADULT LIFE

- GCs are given at replacement and not pharmacological doses, while the influence of
  - Age
  - Gender
  - Laboratory data
  - Patient-specific recommendations for stress
  - Goals of treatment on glucocorticoid replacement therapy

  are seriously taken into consideration

# Adverse Effects of Hypercortisolemia

Prolonged GC substitution therapy may lead to:

Hypercortisolemia with the resultant well-documented adverse effects on every aspect of metabolism, especially

- Growth
- Fat distribution
- Insulin resistance
- Psychological profile

# Major disadvantages of Prolonged GC substitution therapy

- Lack of an adequate clinical index or biochemical marker of adequate replacement dosage, such as exist regarding TSH values in hypothyroidism
- Because of frequent daily dosing of hydrocortisone, most adult endocrinologists prefer either dexamethasone or prednisolone, at appropriate doses
- Equivalence of different GCs is based on
  - Their anti-inflammatory action not on different aspects of human metabolism

# Diverse responses of different GCs in various tissues

- Cortisol affects almost 20% of the human genome
- Dexamethasone →deterioration of indices of insulin resistance in comparison to other GCs
- Long standing use of prednisolone (2.5 –7.5 mg) → negative impact on bone metabolism
- Hydrocortisone should be considered the best in cases of GC supplementation therapy

The advent of the newly synthesized hydrocortisone formula with one pill per day and its initial positive results in patients with CAH shows much promise for the future ).

# Management During Childhood

- Hydrocortisone 10–15 mg/m$^2$, divided into three doses or lower doses starting from 6 mg/m$^2$/day
- In precocious puberty GnRH analog is added
- GH is added if growth velocity < 4 cm/yr or if the predicted final height (PFH) SDS is -2.25 or PFH is 10 cm below their midparental height
- Androstenedione and testosterone levels should be maintained in the mid to upper

- According to some papers, suppression of 17 OHP and progesterone levels requires very high GC doses and it is written that:
- 17 OHP values are crucial for the diagnosis, but not helpful during follow–up
- But if the highest dose be applied at night (according Maria New recommendation) 17 OHP will become low and can be a hallmark of good control
- Blood sampling for hormonal evaluation must be carried out without cessation of therapy

# Management During Adolescence in Patients Treated Since Childhood

- there are no specific guidelines for the timing of regimen changes or cessation of glucocorticoid therapy in children

- Until the establishment of the normal menstrual pattern in NCCAH girls, the continuation of GCs that started during childhood is highly recommended

# Management During Adolescence in Patients Treated Since Childhood

- If there are severe hyperandrogenic findings, such as hirsutism, acne, and or oligomenorrhea, continuation of treatment will be considered

# Treatment of females with hyperandrogenic symptoms as first manifestation during adolescence or after treatment discontinuation

- 6 to 12 months oral contraceptive pills (OCPs)
  - Increase of SHBG liver production
  - Decrease of androgen release from the ovary

Clinical improvement following at least 2–3 months of OCPs initiation

The concurrent use of a progestagen with minimal androgenic properties is highly

If OCPs fail as the first line approach,

Antiandrogens (spironolactone, flutamide, bicalutamide, cyproterone acetate, and finasteride) may be added to the treatment

In some experiences, the administration of bicalutamide has achieved significant improvement in cases of severe acne, but similar results were not obtained in cases with severe hirsutism

- Cosmetic approaches such as laser application

and depilatories can also be suggested for women complaining of excessive or unwanted hair growth

- GCs is highly recommended:
  - In patients with inadequate cortisol secretion after ACTH stimulation
  - If OCPs and antiandrogens cannot be tolerated, or ineffective

- Data from New et al. indicate that irregular menses and acne are reversed within 3 months after the initiation of the glucocorticoid therapy, whereas hirsutism requires nearly 30 months

- By contrast to childhood, in adolescence, longer-acting steroids are often used and regimens of 5mg of prednisolone or 0.25mg of dexamethasone are used. However, in the real world clinical data have shown a variety of different regimens applied in NCCAH management.

- According to the Endocrine Society guidelines, NCCAH patients should be given the option to discontinue GC therapy when symptoms resolve

- Of course, these patients should not be lost to follow-up, while treatment should be reinitiated in the event of recurrence of the symptoms.

- Further, in the case of discontinuation, patients should be informed about the possibility of infertility and should encouraged to seek medical advice if they wish to conceive

- Of note, the appropriate transfer of the patient from the pediatric to the adult endocrinologist should be carried out, optimally after 1 year of synchronized

# Stress Management in NCCAH

During major life-threatening stress, surgery, or serious illness, patients with NCCAH who are glucocorticoid-treated may require larger or more frequent doses of glucocorticoids given that their adrenal function is iatrogenically suppressed

# ACTH Test

- For NCCAH patients who are not treated with GCs or in the event of discontinuation, basal cortisol and response to ACTH should be assessed

- Basal value 415 nmol/l (15 µg/dl) of cortisol needs ACTH stimulation test

- If peak cortisol after ACTH stimulation test is below 496 nmol/L (18 µg/dL), steroid treatment should be administered in cases of stress even if they are not treated with corticosteroid

# Stress Management in NCCAH

- For those who respond normally to ACTH no stress dose is recommended
- Mineralocorticoid therapy is not required in any of the cases with NCCAH
- A psychological diagnosis and support also need to be offered.
- Almost one third of NCCAH patients respond inadequately to the ACTH stimulation
- It is crucial to educate the parents of young children, as well as to re-educate patients on their transition to adult care, about stress dosing

We reviewed medical records of 617 patients with CAH who were referred to us during 43 years

## Frequency of different types of CAH (1968 -2011)

| type | Gender according to karyotype n (%*) | | total n (%**) |
|---|---|---|---|
| | female | male | |
| 21-OHD | 300(61) | 191 (39) | 491 (79.6) |
| 11-OHD | 39 (48) | 43 (52) | 82(13.3) |
| 3-βOHD | 6 (24) | 19 (76) | 25 (4.1) |
| lipoid | 3 (43) | 4 (57) | 7 (1.1) |
| 17-OHD | 5 (83) | 1 (17) | 6 (1) |
| hypoaldo | 2 (50) | 2 (50) | 4 (0.6) |
| ABS | 1 + 1 T | 0 | 2 (0.3) |
| Total | 356 (58), 1 T | 260 (42) | 617(100) |

# Frequency of different types of 21-hydroxylase deficiency

| Gender | Types of 21-OHD Count (%) | | | | |
|---|---|---|---|---|---|
| | Classic | | | Non Classic | Total |
| | SW | SV | Total | | |
| Female | 211 (58) | 65 (64) | 276 (59.5) | 24 (89) | 300 (61) |
| Male | 151 (42) | 37 (36) | 188 (40.5) | 3 (11) | 191 (39) |
| Total | 362 (78) | 102 (22) | 464 (94.5) | 27 (5.5) | 491(100) |

SW, salt wasting; SV, simple virilizing


Thank you for your attention