ENDOCRINE DISORDERS

Congenital Adrenal Hyperplasia (CAH)

What is Congenital Adrenal Hyperplasia (CAH)?

CAH is a group of disorders resulting from enzymatic defects in the biosynthesis of steroids. There are many enzymes involved in the synthesis of adrenal hormones but 21-hydroxylase deficiency is the most common. Others are due to cholesterol desmolase 11ß-hydroxylase deficiency, 17ß-hydroxylase deficiency, and 3ß-hydroxysteroid dehydrogenase. The Philippine NBS data as of December 2021 reports that 1 out of 20,589 screened newborns have CAH.

PATHOPHYSIOLOGY

Adrenal steroidogenesis occurs in three major pathways as shown in Figure 1. Aldosterone is produced in the zona glomerulosa; glucocorticoids (particularly cortisol) in the zona fasciculata; and androgens in the zona reticularis. The hypothalamic-pituitary-adrenal feedback system is mediated by the circulating level of cortisol. A decrease in cortisol secretion leads to increased ACTH production which in turn stimulates the synthesis of the adrenal products in those pathways unimpaired by the enzyme deficiency and an increase in the precursor molecules blocked by the enzymatic deficiency.

CAH is a group of autosomal recessive disorders characterized by impaired cortisol synthesis. The most common form of CAH is caused by mutations in CYP21A2, the gene encoding the adrenal steroid 21-hydroxylase enzyme (P450c21) that accounts for approximately 95% of CAH. The decreased cortisol and aldosterone production causes increased ACTH production which in turn results in hyperplasia of the adrenal cortex. About 75% of classic CAH patients have aldosterone deficiency. The precursor steroids prior to the block are diverted to the androgen biosynthetic pathway resulting in excess production of androgens.

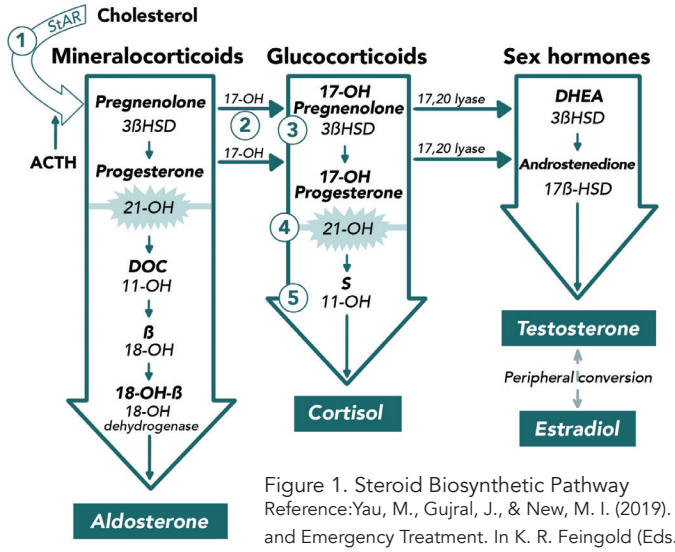

Figure 1. Steroid Biosynthetic Pathway
Reference:Yau, M., Gujral, J., & New, M. I. (2019). Congenital Adrenal Hyperplasia: Diagnosis and Emergency Treatment. In K. R. Feingold (Eds.) et. al., Endotext. MDText.com, Inc.

CLINICAL MANIFESTATIONS

1. Classical Salt-Wasting CAH

- In the first 2-4 weeks of life, the neonate may be asymptomatic but about 75% have aldosterone deficiency manifesting with salt-wasting adrenal crisis characterized by poor feeding, vomiting, loose stools or diarrhea, lethargy, weak cry, dehydration, failure to thrive, hyperpigmentation, potentially fatal hypovolemia, and shock depending on the severity of 21- hydroxylase deficiency
- Affected females usually present with mildly ambiguous/ atypical to completely virilized external genitalia at birth which is a cardinal feature of classical CAH; Internal genitalia (ovaries, uterus, and fallopian tubes) are not affected
- Affected males do not manifest with genital abnormalities at birth
- If the neonate with severe 21-hydroxylase deficiency is unrecognized and untreated, the affected newborn will die due to a severe salt-wasting crisis accompanied by hypoglycemia and hypotension
- In untreated males and females, excessive androgen production results in progressive penile or clitoral enlargement, hirsutism, acne, deepening of the voice, alopecia, tall stature in early childhood with ultimate short stature

2. Classical simple virilizing CAH

- Presents similarly to the salt-wasting type except that there are no severe or life-threatening adrenal crisis in the newborns but they have hyperpigmentation
- Females are identified later in childhood because of the early development of pubic hair, clitoromegaly, or both, often accompanied by accelerated growth and skeletal maturation
- Males present later in childhood with the early development of pubic hair, phallic enlargement, or both accompanied by accelerated linear growth and advancement of skeletal maturation

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3. Non-classical CAH

- Late-onset form of CAH
- Clinical symptoms show variable degrees of postnatal androgen excess and maybe asymptomatic
- Females may present in adolescence or adulthood with oligomenorrhea, hirsutism, and or infertility
- If untreated, affected males and females may have early onset of pubic hair and rapid somatic growth

Diagnosis

The diagnosis of CAH is confirmed by an elevated plasma 17-hydroxyprogesterone (17OHP). Ancillary laboratory tests include levels of Na, K, cortisol, and RBS. In patients whose 17OHP values are not conclusive, a corticotropin stimulation test is done. If it cannot be accurately performed, genotyping is suggested.

Above workups are done when CAH is highly considered as in the case of the following:

1. In all newborns with ambiguous genitalia to rule out classic virilizing and/or salt-wasting CAH without waiting for the result of the newborn screening in anticipation of a possible adrenal crisis within the first few days of life. Karyotyping and pelvic sonography are ancillary procedures necessary to establish the genetic sex of the baby to avoid wrong sex assignment and check the internal reproductive structures respectively.
2. Among infants with grossly normal genitalia but positive for CAH in the newborn screening.
3. Precocious puberty among boys manifests as precocious pubic hair, excessive growth, and premature phallic enlargement in the absence of testicular enlargement.
4. Among females with hirsutism, oligomenorrhea, or infertility
5. In those patients manifesting with signs of adrenal crisis, additional workups such as blood gas analysis are necessary.

Treatment of Classical CAH

- Glucocorticosteroids – Hydrocortisone is the drug of choice. It is preferred over other long-acting, more potent steroids because of its less growth-suppressive effect.
  - Dose: 10-15 mg/m2/day in 3 divided doses
  - Dose is increased during periods of stress like fever >38.5°C, gastroenteritis with dehydration, major surgery, and trauma.
  - Stress doses of hydrocortisone for adrenal crisis:
    - 25mg for infants & preschool children
    - 50mg for school-age children
    - 100mg for adults
    - After the above dose, successive doses are given at 4 divided doses
- Mineralocorticoid – Fludrocortisone
  - Dose: 0.05-0.2 mg/day, with dose requirement decreasing with age
- Sodium chloride tablets supplementation
  - Dose: 1-2 g/day
- Surgical repair of external genitalia – for females with ambiguous genitalia

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Monitoring

- Frequency:
  - Close monitoring during the first 3 months of life
  - Quarterly during the 1st 1-2 years.
  - Every 4 months for infants beyond 18 months.

- Signs & symptoms to watch out for
  - Excessive glucocorticoid use (Cushingoid features, poor growth, excessive weight gain, hypertension)
  - Excessive mineralocorticoid use (tachycardia, hypertension)
  - Undertreatment ((elevated 17OHP, low Na, high K, hyperpigmentation, virilization, advanced bone age, increased growth velocity, early puberty for boys)

- Laboratory tests to be requested
  - 17 hydroxyprogesterone
  - Sodium
  - Potassium
  - Plasma renin activity (PRA)
  - Bone aging

Prognosis

Newborn screening makes early diagnosis and early treatment possible. Early treatment to prevent an adrenal crisis is lifesaving in cases of salt-wasting CAH. In newborns with ambiguous genitalia, early diagnosis prevents incorrect sex assignment. This is important due to the psychological and legal implications of wrong gender assignments. Progressive effects of excess androgens such as short stature and psychosexual disturbance in male and female patients are also prevented if appropriate treatment is given and monitored closely. Psychological support is equally important.

Adequate treatment, regular monitoring, and follow-up with a specialist are important to prevent consequences such as adrenal crisis, excessive virilization, precocious puberty in males, short stature, and psychological issues.

References:

Speizer PW., Artl W., Auchus RJ., Baskin LS., et al. Congenital Adrenal Hyperplasia due to Steroid 21 Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. JCEM 103(11):1-46, 2018.
Mabel Yau, MD, Jasmine Gujral, MD, and Maria I New, MD. Congenital Adrenal Hyperplasia: Diagnosis and Emergency Treatment, April 16, 2019.