ENDOCRINE DISORDERS

Congenital Adrenal Hyperplasia (CAH)

What is Congenital Adrenal Hyperplasia (CAH)?

CAH is a group of autosomal recessive disorders characterized by a deficiency of cortisol due to enzymatic defects in the biosynthesis of steroid hormones. Among the many enzymes involved in the synthesis of adrenal hormones, deficiency in 21-hydroxylase is the most common cause accounting for approximately 95% of CAH. The decreased cortisol and aldosterone production causes increased ACTH production in the pituitary resulting to hyperplasia of the adrenal cortex. The Philippine NBS data as of December 2022 reports that 1 out of 20,700 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.

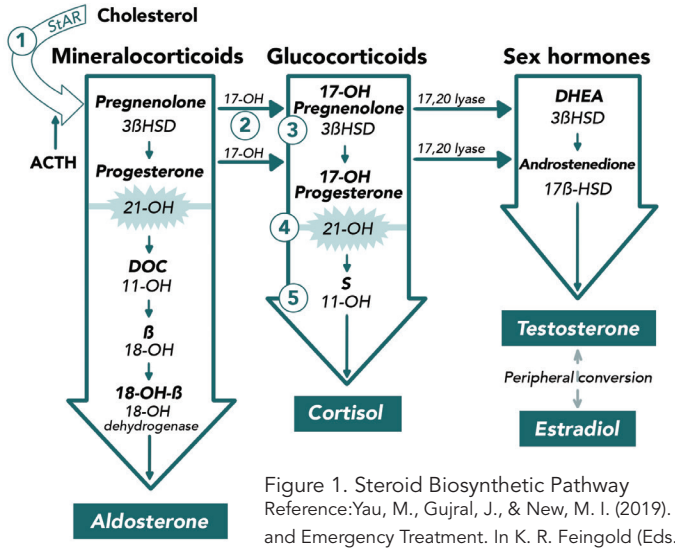

Figure 1. Steroid Biosynthetic Pathway
Reference:Yau, M., Gujral, J., & New, M. I. (2019). Congenital Adrenal Hyperplasia: Diagnosis and Emergency Treatment. In K. R. Feingold (Eds.) et. al., Endotext. MDText.com, Inc.

CLINICAL MANIFESTATIONS

1. Classical salt-wasting CAH

- The cardinal feature of classical CAH is virilization wherein females present with mildly atypical external genitalia to completely virilize at birth. Ovaries, uterus, and fallopian tubes are not affected.
- Males do not manifest with genital abnormalities at birth but may demonstrate hyperpigmentation.
- By 2 weeks of life, if unrecognized, the newborn will manifest weak cry, lethargy, poor feeding and failure to thrive. If still untreated, the infant will go into a salt-wasting adrenal crisis characterized by vomiting, diarrhea, dehydration and hypoglycemia which can lead to potentially fatal hypovolemia, hypotension and shock.

2. Classical simple virilizing CAH

- Females have atypical genitalia but do not have severe or life-threatening adrenal crisis.
- Males present later in childhood with the early development of pubic hair, penile enlargement, or both accompanied by accelerated linear growth and advancement of skeletal maturation.

ENDOCRINE DISORDERS

Congenital Adrenal Hyperplasia (CAH)

Diagnosis

An elevated plasma 17-hydroxyprogesterone (17OHP) confirms the diagnosis of CAH. Ancillary laboratory tests include levels of Na, K, RBS and cortisol. In patients whose 17OHP values are not conclusive, a corticotropin (ACTH) stimulation test should be performed. If not feasible, genotyping is suggested.

For atypical genitalia, the following should be done:

1. karyotyping
2. pelvic ultrasound to include inguino-labioscrotal folds

Long–term treatment

1. 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 doubled during periods of stress like fever >38.5oC, gastroenteritis with dehydration, major surgery, and trauma.
   - Stress doses of hydrocortisone during adrenal crisis:
     - Infants & preschool children: 25 mg
     - School-age children: 50 mg
     - Adults: 100 mg
     - After the above dose, succeeding doses are given in 4 divided doses
2. Mineralocorticoid – Fludrocortisone
   Dose: 0.05-0.2 mg/day, with dose requirement decreasing with age
3. Sodium Chloride tablet supplementation
   Dose: 1-2 g/day
4. Surgical repair of external genitalia for females with atypical genitalia
5. Family counseling

Monitoring

1. 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.

2. Signs & symptoms to watch out for
   a. Excessive glucocorticoid use
   -Cushingoid features, poor growth, excessive weight gain, hypertension
   b. Excessive mineralocorticoid use
   -tachycardia, hypertension
   c. Undertreatment
   -hyperpigmentation, virilization, increased growth velocity, early puberty in boys

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

Prognosis

Newborn screening makes early diagnosis and prompt treatment possible. Early treatment to prevent adrenal crisis is lifesaving in cases of salt-wasting CAH. In newborns with atypical genitalia, early diagnosis prevents incorrect sex assignment. This is important due to the psychological and legal implications of wrong gender assignment.

With adequate treatment, regular monitoring, and follow-up with a specialist, adrenal crisis, virilization, precocious puberty in males, short stature, and psychological issues may be prevented.

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.