CONGENITAL HYPOTHYROIDISM

It is a **common & serious disease**, its prevalence is 1/4,000 infants,
Et. Cong hypothyroidism is either **Primary** (most common) due to defects in the thyroid gland or thyroid hormone receptors, or **Central** (Hypopitutarism)
C.M. Most infants with cong hypothyroidism are **asymptomatic at birth** (may be due to transplacental passage of maternal T_4), thus early Dx is depend on **neonatal screening tests**, otherwise physician must always have **high index of suspicion** about early manifestations of cong hypothyroidism.

Hx. Lethargy, sleepy, poor hoarse cry, poor appetite & feeding, apnea, noisy respiration, constipation, & prolonged jaundice (due to delayed maturation of glucuronide conjugation).
Ex. Dysmorphic features include: open mouth, large protruded tongue, hypertelorism, depressed nasal bridge, short and thick neck, and fontanels are widely opened.
Other features include: birth weight & length are **normal**, head size is normal or slightly increased, **hypothermia** (temp < 35°C), **bradycardia** +/_ heart murmurs, abdominal **distention**, umbilical **hernia**, cold mottled **skin** which is yellow in color (due to carotenemia in addition to jaundice), **myxedema, hypotonia,** & later on, delayed dentition.
Cong hypothyroidism may be associated with other conditions e.g. sensorineural deafness (20%) or CHD (10%).
Cx. Cong hypothyroidism **if untreated in the 1st 3–6 mo of life**, it will **severely affect physical and mental development** → delayed milestone, stunted growth, & delayed sexual maturation.

Investigation

 Neonatal Screening is mandatory. It depend on **measuring serum T4**, if low, **measure TSH**, if high (>100 mU/L), this will confirm primary hypothyroidism.
 CBP usually show **macrocytic anemia** which usually refractory to Rx with hematinics.
 X-ray of knees show absent of distal femoral epiphysis in ≈ 60% of cases, which normally should be present at birth. Epiphyseal dysgenesis usually occurs later on.
Skull X-ray show large fontanels, wide sutures, wormian bones, and enlarged sella turcica.
CXR may show cardiomegaly +/_ pericardial effusion.

 US of neck can detect the site & size of thyroid gland.
 Thyroid scan with radioiodine will reveal its uptake if there is any normal thyroid tissue, whereas **failure of radioiodine uptake suggest** either thyroid aplasia, iodide-trapping defect, or neonates with TRBAb.
 Thyroglobulin level; it ↓ in thyroid aplasia or defects in its synthesis, but ↑ in ectopic glands and goiter.
 Serum Cholesterol level is usually elevated in children > 2 yr.
 ECG & EEG; both show low-voltage.
 MRI is normal in primary hypothyroidism, but may be abnormal in central hypothyroidism.

Rx. Levo-thyroxine (T4) is given orally; initial dose **10–15 µg/kg/day** for neonates & infants, whereas **children dose ≈ 4 µg/kg/day**. A good index of adequacy of Rx is growth rate & change in behavior and activity.

SE of Thyroxine (especially in overdose) are the same that of hyperthyroidism including: craniosynostosis, temperament problems, & pseudotumor cerebri (in older children).
Note: *Oral thyroxine should not be mixed with iron, calcium, or soy protein formulas.*
The **goal** of replacement Rx is to bring levels of **T4 & TSH to normal range** which requires frequent **monitoring** at intervals; **monthly in the first 6 mo** of life, then **every 2–3 mo up to 2 yr**.
This frequent follow-up is also useful in confirmation of persistent cong hypothyroidism to rule out the possibility of transient hypothyroidism.

Pg. Thyroid hormones are **very essential for brain development in the early postnatal months**, thus early Dx & Rx is critical to prevent progressive neuropsychological sequelae.
Note: *If the oncet of hypothyroidism occur **after 2 yr** of age, there may be normal neurological development **even** if Dx & Rx are delayed.*

DIABETES INSIPIDUS

Physiology of Water Balance:-

Extracellular fluid **tonicity** is regulated almost exclusively by **water** intake & excretion mainly through ADH; whereas extracellular **volume** is regulated by **sodium** intake & excretion through renin-angiotensin- aldosterone system & to lesser extent by vasopressin and the natriuretic peptide family.

ADH (Vasopressin) is synthesized in the **hypothalamus** & secreted from the posterior pituitary; its half-life is only **5 min**. In addition to the **antidiuresis**, it has **vasopressor** effect. It secreted in response to: hyperosmolality, hypotention, hypovolemia, hypoglycemia, nausea, & pain.

C.M. DI generally → **polyuria, polydipsia, & dehydration**; additional symptoms in infants include: **irritability, fever, FTT, & constipation.**

Note: *Any patient with long standing polyuria may develop non-obstructive hydronephrosis, hydroureter, and megabladder.*

D.Dx. DM & Psychogenic (primary) polydipsia.

❖ *Approach to patient with polyuria & polydipsia**:-***

Polydipsia means **excessive thirst** with fluid intake **> 2 L/m$_2$/day**.

Polyuria is evaluated by **quantity of urine, nocturia, & enuresis**.

In addition to evaluation of hydration status due to ADH deficiency, patient should be evaluated for other pituitary hormone deficiencies, and visual & CNS dysfunction.

Inv.

1. Exclude **Psychogenic** polydipsia by hx.

2. Exclude **DM** by serum & urine glucose level.

3. Do the following tests; **serum** osmolality, sodium, potassium, urea, creatinine, and calcium; as well as **urine** osmolality & specific gravity.

❖ ***Diagnostic Criteria for DI:-***

Serum osmolality **> 300** mOsm/kg, Urine osmolality **< 300** mOsm/kg associated with **Hypernatremia** (serum Na > 155 mg/dL).

In equivocal cases, do ***Water Deprivation Test*** to establish Dx of DI and to differentiate between central & nephrogenic causes; this also can be done by ***administration of ADH***.

DI can be devided into Central & Nephrogenic; each can be caused by Genetic or Acquired causes.

Central Diabetes Insipidus

Et.

- **Genetic mutations** e.g. AD central DI
- **Congenital Brain Abnormalities**
- **Trauma (accidental or surgical)**
- **Infections** e.g. meningitis, cong CMV infection.
- **Tumors & Infiltrations*:***

Infiltrative disorders include: AML, Langerhans cell histiocytosis, & Lymphocytic Hypophysitis (which acounts ≈ 50% of "idiopathic" central DI).

- **Drugs** that inhibit vasopressin release are: ethanol, halothane, phenytoin, opiate antagonists, and α-adrenergic agents.

Note: *10% of cases are idiopathic & it may be associated with other pituitary hormone deficiencies.*

Rx.

- ***Fluid therapy;*** It can be the sole Rx for **neonates and young infants** through **free access to oral fluids** due to their requirement to a large amounts of nutritive fluid that may reach up to 3 $L/m^2/24$ hr.
- ***Vasopressin Analogs*** e.g. long-acting vasopressin analog **dDAVP (desmopressin)** as nasal spray or oral tablet; it suitable for **older children.**

SE of Vasopressin are Water intoxication

Nephrogenic Diabetes Insipidus

Et.

- **Genetic mutations** are less common but more severe e.g. ***Congenital X- linked NDI*** (most common) as well as AR & AD NDI.
- **Hypercalcemia & Hypokalemia.**
- **Impaired renal concentrating ability** e.g. ureteral obstruction, chronic renal failure, polycystic kidney disease, medullary cystic disease.
- **Drugs** e.g. lithium, demeclocycline, foscarnet, clozapine, amphotericin, methicillin, and rifampin.
- ↓ protein or sodium intake or excessive water intake (e.g. primary polydipsia) can also cause NDI!.

Rx.

- **Acquired causes** of NDI e.g. hypercalcemia, hypokalemia, offending drugs, or ureteral obstruction should be **eliminated.**
- **Congenital NDI** is often **difficult** to treat; however, the main goals are to ensure intake of **adequate calories for growth** and to **avoid**

severe dehydration by free access to water & nutritive fluids. Foods with highest ratio of caloric content to osmotic load should be ingested e.g. Similac PM 60/40. Many infants may require **NG tube or gastrostomy** to ensure adequate fluid & calories administration.
 Pharmacologic Rx for NDI include: **Thiazide diuretic** (2-3 mg/kg/day) effectively induce sodium excretion at the expense of water with water reabsorption. If there is no adequate response, add **Indomethacin** in combination with **Amiloride** or **High-dose dDAVP.**
Pg. Unfortunately, many patients with congenital NDI are subjected to
Cxs **even** after institution of early Rx e.g. growth failure, behavioral abnormalities, & mental retardation

CONGENITAL ADRENAL HYPERPLASIA

AH is a family of **AR disorders of cortisol biosynthesis**. Cortisol deficiency increases secretion of ACTH, which in turn result in adrenocortical hyperplasia and overproduction of the intermediate metabolites. Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess; incomplete virilization or premature puberty in affected males; and virilization or sexual infantilism in affected females.

CAH due to 21-Hydroxylase Deficiency

Et. It accounts **>90%** of CAH cases. It caused by deficiency of 21-hydroxylase which is a P450 enzyme (CYP21, P450c21) that hydroxylates progesterone & 17-hydroxyprogesterone (17-OHP) to yield 11-deoxy- corticosterone (DOC) & 11-deoxycortisol respectively, which eventually yield aldosterone and cortisol respectively.
Path. It can be divided into classical & non-classical.
 Classical *21-hydroxylase deficiency* involve either deficiency both hormones (i.e. aldosterone and cortisol) in the most **severe** form **(70%)** of disease ***"Salt-wasting"***, or the patients are able to synthesize adequate amounts of aldosterone in the **less severe** form **(30%)** of disease; but they also have elevated levels of androgens of adrenal origin, thus called ***"Simple virilizing disease"***.
 Non-classical *disease*, which is **more common** than classical one, patients have only mild elevation of androgens and may have signs of androgen excess after birth.

C.M.

❖ Patients with **Classic disease** have the following manifestations:-

 Aldosterone and Cortisol deficiency: Both hormones are deficient in *"salt-wasting"* disease → **anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia, hyperkalemia, and progressive weight loss.** These problems are typically develop as early as **10-14 days** of life & if patient is untreated; shock, cardiac arrhythmias, and death may occur within days or weeks.

 Prenatal Androgen Excess: The steroid precursors are accumulated up to **hundreds times of normal** including **17-OHP & progesterone**. 17- OHP is shunted into the pathway of **androgen biosynthesis** → high levels of androstenedione which converted outside the adrenal gland into testosterone.

This problem begins as early as **8-10 wk of gestation** → masculinized of external genitalia of the affected **female** e.g. **enlargement of clitoris** with partial or complete **labial fusion**. The vagina usually has a common opening with the urethra (urogenital sinus); however, the internal genital organs are **normal** as female.

Note: *Since urethra opens below urogenital sinus, some affected females may mistakenly presumed to be males with hypospadias & cryptorchidism.*

Male infants appear normal at birth, thus, Dx may not be made in them until signs of adrenal insufficiency develop, whereas those with simple virilizing form have even more delay in Dx because they appear normal and rarely develop adrenal insufficiency. Hence, newborn screening is essential in every infant by measuring 17-OHP at birth.

❖ Patients with **Non-classical** 21-hydroxylase deficiency **show similar but milder signs of androgen excess**. In this attenuated form, cortisol and aldosterone levels are **normal** and affected females have normal genitals at birth. However later in life, females and males either remain **asymptomatic** or may present with signs of **precocious pubarche** e.g. early development of pubic and axillary hair, hirsutism, acne, and in females, menstrual disorders and infertility may occur.

Inv.

 Patients with salt-losing disease have typical laboratory findings associated with **cortisol & aldosterone deficiency** e.g. **hyponatremia, hyperkalemia, metabolic acidosis, and often hypoglycemia**, but these abnormalities can take 10-14 days or longer to develop after birth.

 Blood levels of 17-OH Progesterone are markedly elevated.
 Androstenedione & testosterone are also elevated in affected females; whereas in male infants, testosterone is not usually elevated because it is already in high level normally.
 Blood levels of **cortisol** are usually low in patients with salt-losing type, whereas it is often normal in patients with simple virilizing disease (although inappropriately low in relation to ACTH and 17-OHP levels).
 Genotyping

❖ ***Approach to patient with ambiguous genitalia:-***

A thorough **physical exam** to define the anatomy of the genitals including palpation of scrotum (or labia) and the inguinal regions for **testes**, if it present, it **almost always** indicate that the infant is **genetically male**.
US is helpful in demonstrating the presence or absence of uterus and can often locate the gonads (ovaries or intra-abdominal testes).
Rapid **karyotype** e.g. FISH technique can quickly determine the genetic sex of the infant.
 Prenatal diagnosis of 21-hydroxylase deficiency is usually done when the parents have **already an affected child**

Rx.
 Glucocorticoid Replacement Therapy:- **Glucocorticoid Rx must be continued indefinitely in all patients with classical disease but may not be necessary in non-classical disease** unless signs of androgen excess are present.

• ***Mineralocorticoid Replacement Therapy:-***
Patients with **salt-wasting disease**, i.e. aldosterone deficiency, require mineralocorticoid replacement with **fludrocortisone**

CAH due to 11β-Hydroxylase Deficiency

All signs and symptoms of androgen excess that are found in 21-hydroxylase deficiency usually also occur in 11-hydroxylase deficiency.it is unusual for patients to manifest signs of adrenal insufficiency e.g. hypotension, hypoglycemia, hyponatremia, and hyperkalemia. In contrast, **≈ 65% of patients become hypertensive** (although this can take several years to develop

Inv. Plasma levels of cortisol is low, consequently, ACTH level is high.
11- deoxycortisol and deoxycorticosterone are elevated

Rx. Hydrocortisone is given in doses **similar** to those used for 21-hydroxylase deficiency. **Mineralocorticoid** replacement is sometimes transiently required in infancy
Hypertension often resolves with glucocorticoid Rx but may require additional therapy if it is of long standing by calcium channel blockers.

Addison disease
It is autoimmune disease lead to destruction of the adrenal cortex
Which end in glucocorticoid and mineralocorticoid deficiency

C.M :hyperpigmentation ,salt craving ,postural hypotention ,fasting hypoglycemia,anorexia and even shock during illness

Investigations:
Hyponatremia ,hyperkalemia and increase renine activity

Treatment;
Replacement of glucocorticoid with 10-15 mg /m2/24hr
Hydrocortisone during stressful condition then kept on maintenance dose
Mineralocorticoid replacement depending on renine activity and electrolyte levels.