Congenital Hypothyroidism

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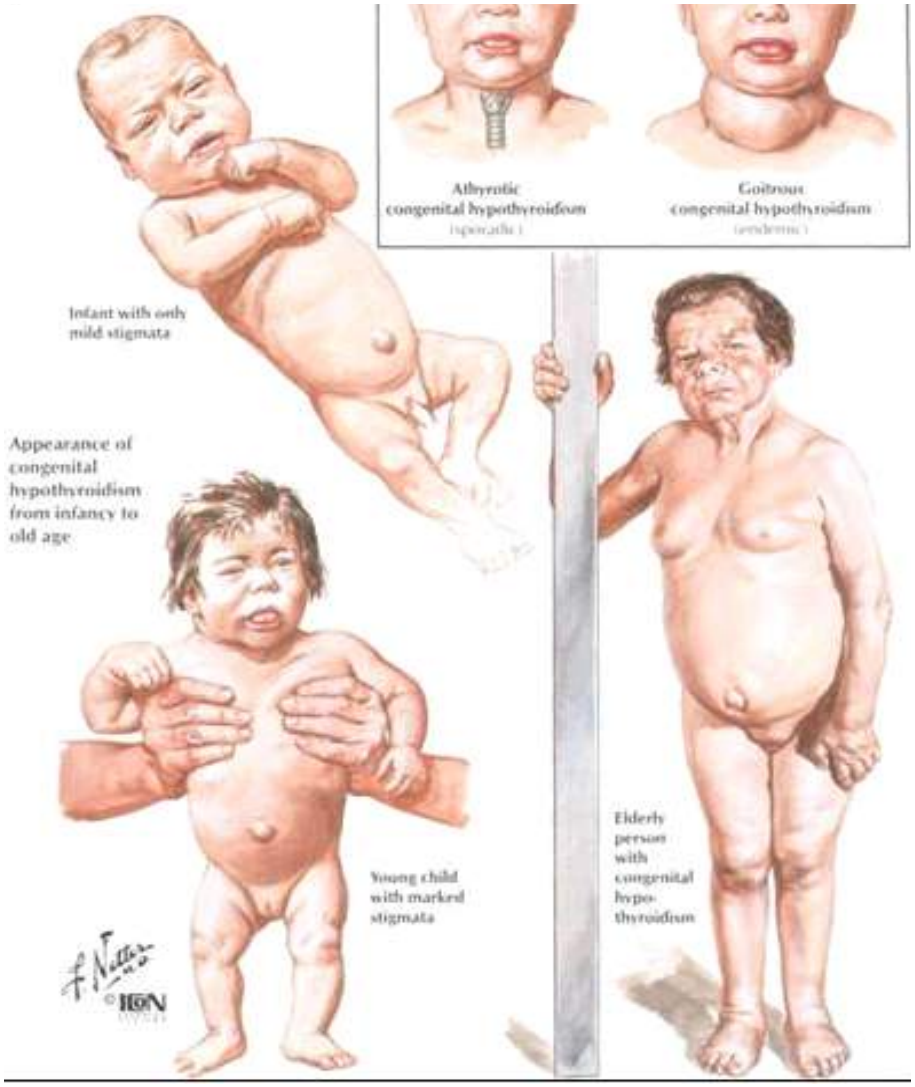
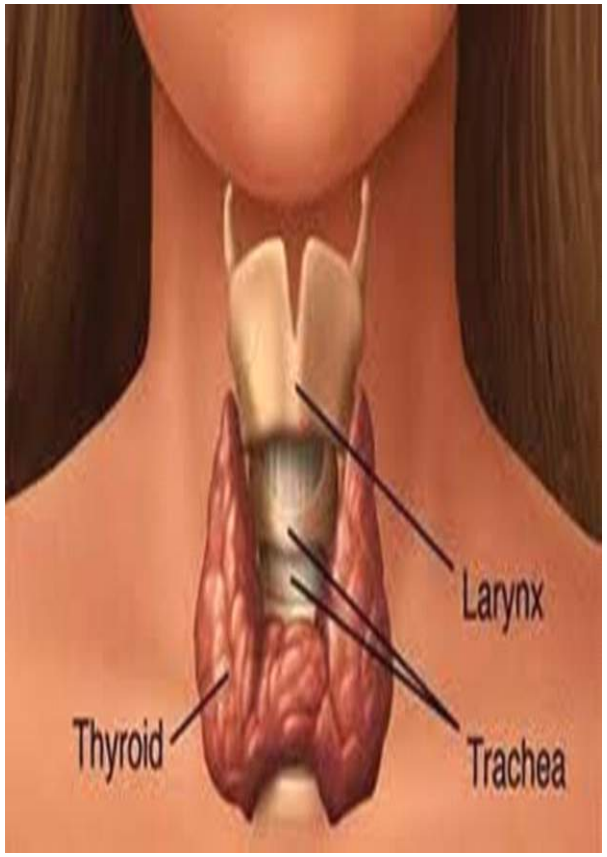


- Introduction
- Anatomy
- Development
- Thyroid hormones
- Congenital Hypothyroidism



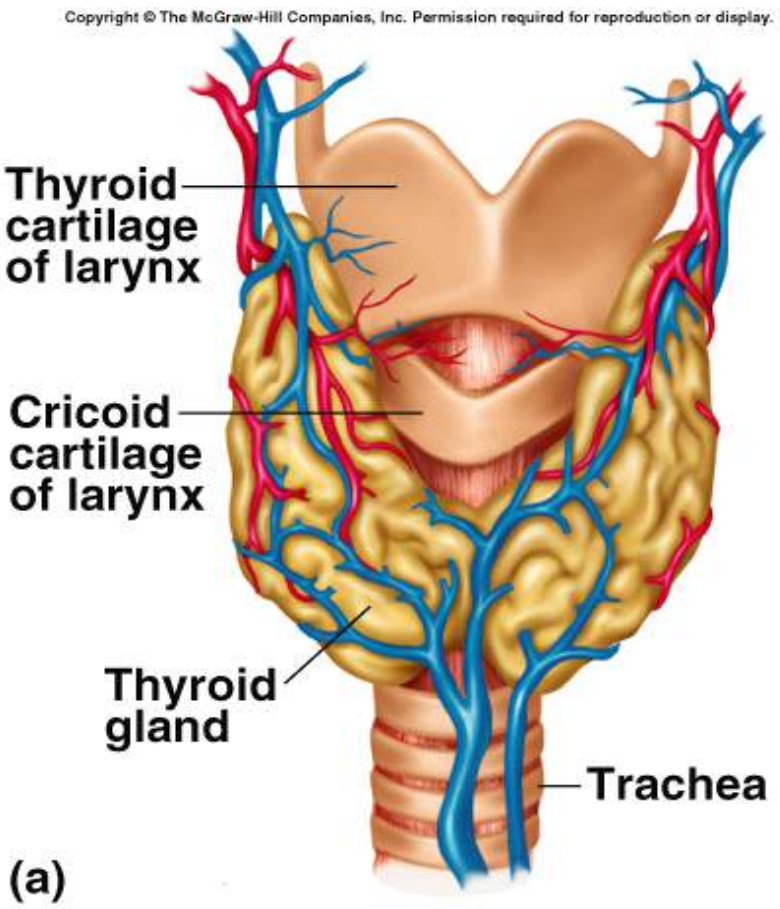
Anatomy

•Thyroid gland (Greek *thyreos*, shield, plus *eidos*, form) is a large unpaired gland situated in the anterior part of the neck.

• The thyroid consists of two lobes connected by an isthmus.

• It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch.

•The normal thyroid is **12–20 g** in size.



Development of Thyroid

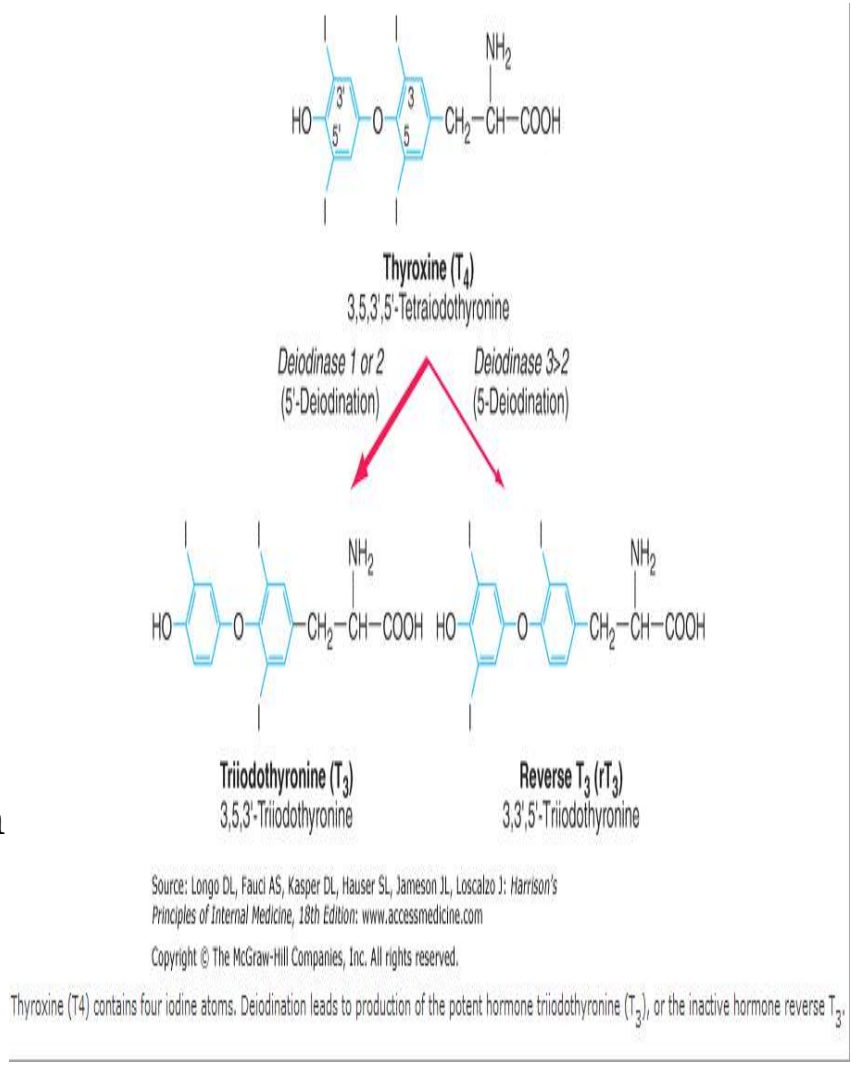
•It develops as an endodermal outpouching from the floor of the pharynx during the 3rd week of gestation, at a site that persists as foramen caecum in the base of the tongue of the adults.

•Thyroglobulin synthesis	- 4 wks gestation
•Iodine trapping occurs	- 8-10 wks gestation
•Synthesis of TRH (produced by hypothalamus)	-6-8 wks gestation
•Fetal thyroid bilobed stucture recognised	-7 wks gestation
•Characteristic thyroid follicular cells and colloid formation	-10 wks gestation
•Synthesis of TSH	**-12 wks gestation**
•Synthesis of thyroxin(T4) and to a lesser extent T3	**-12 wks gestation**

THYROID HORMONES

•About 93 per cent of the metabolically active hormones secreted by the thyroid gland is thyroxine,(T4) and 7 per cent triiodothyronine *(T3)*.

•Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine.



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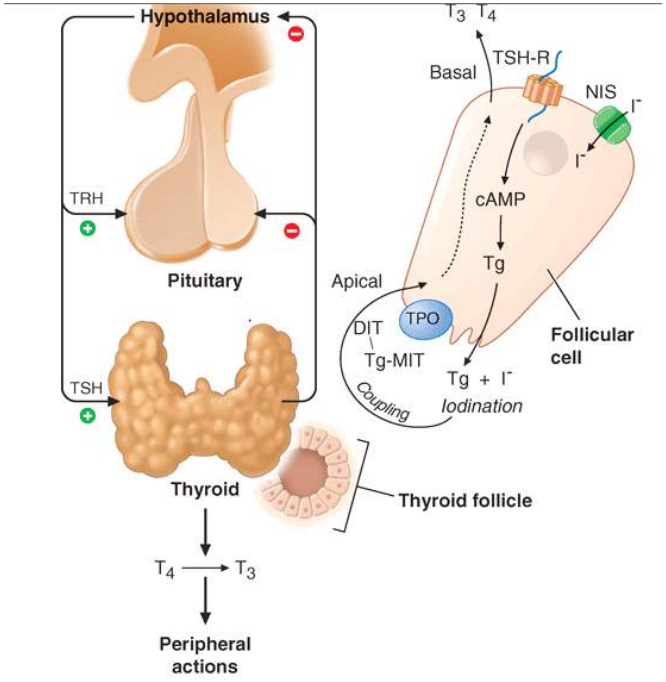
Regulation of thyroid hormone synthesis

•Hypothalamic TRH stimulates pituitary production of TSH which, in turn, stimulates thyroid hormone synthesis and secretion.

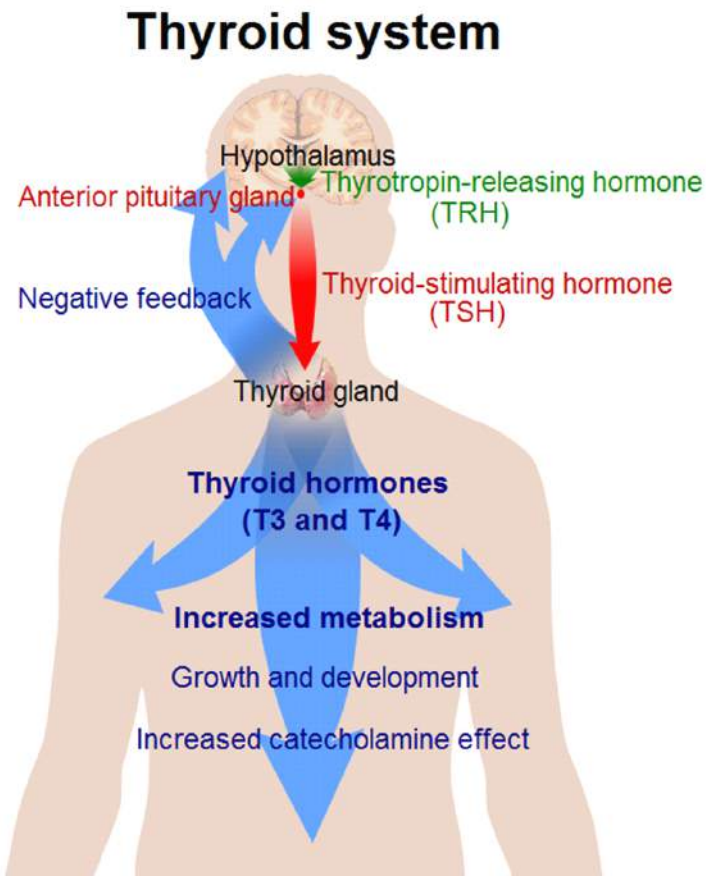
•TSH is the most useful physiologic marker of thyroid hormone action.

• Thyroid hormones acting predominantly through thyroid hormone receptor feedback to inhibit TRH and TSH production

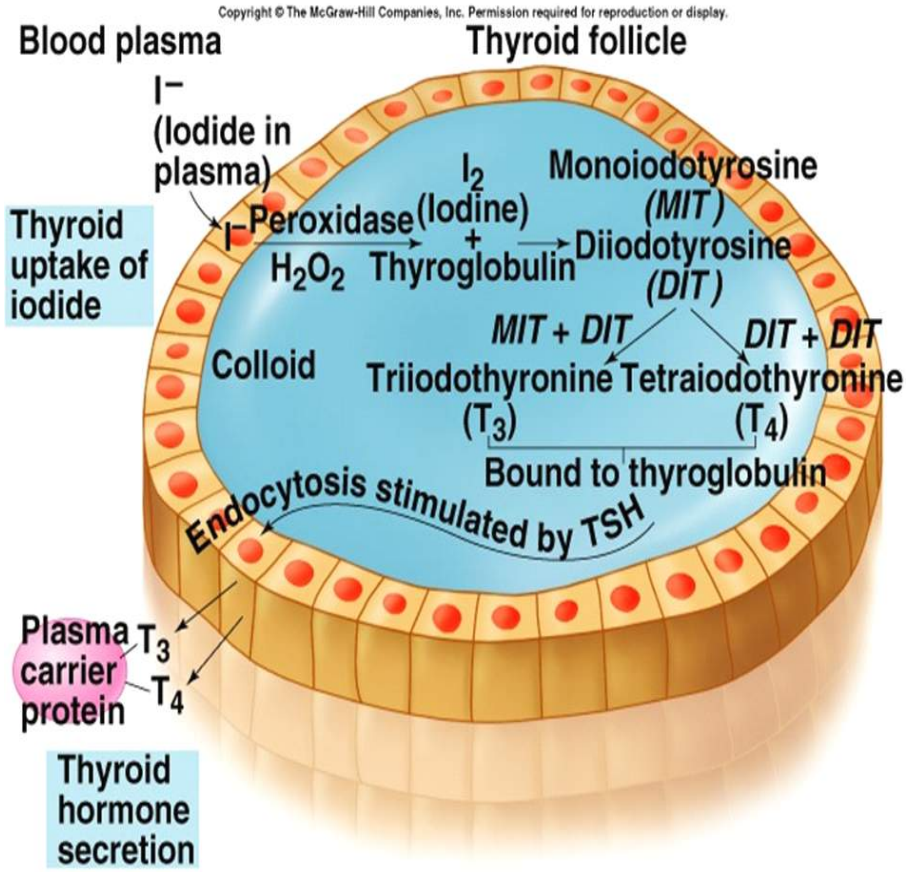


Functions of thyroid hormones

- Brain Maturation
- Increase basal metabolic rate.
- Stimulate protein synthesis
- Influence growth and differentiation of all cells in the body and
- Help to regulate skeletal growth (synergistic with growth hormone)
- Affect carbohydrate, lipid, and vitamin metabolism
- Increase oxygen consumption



THYROID HORMONE SYNTHESIS



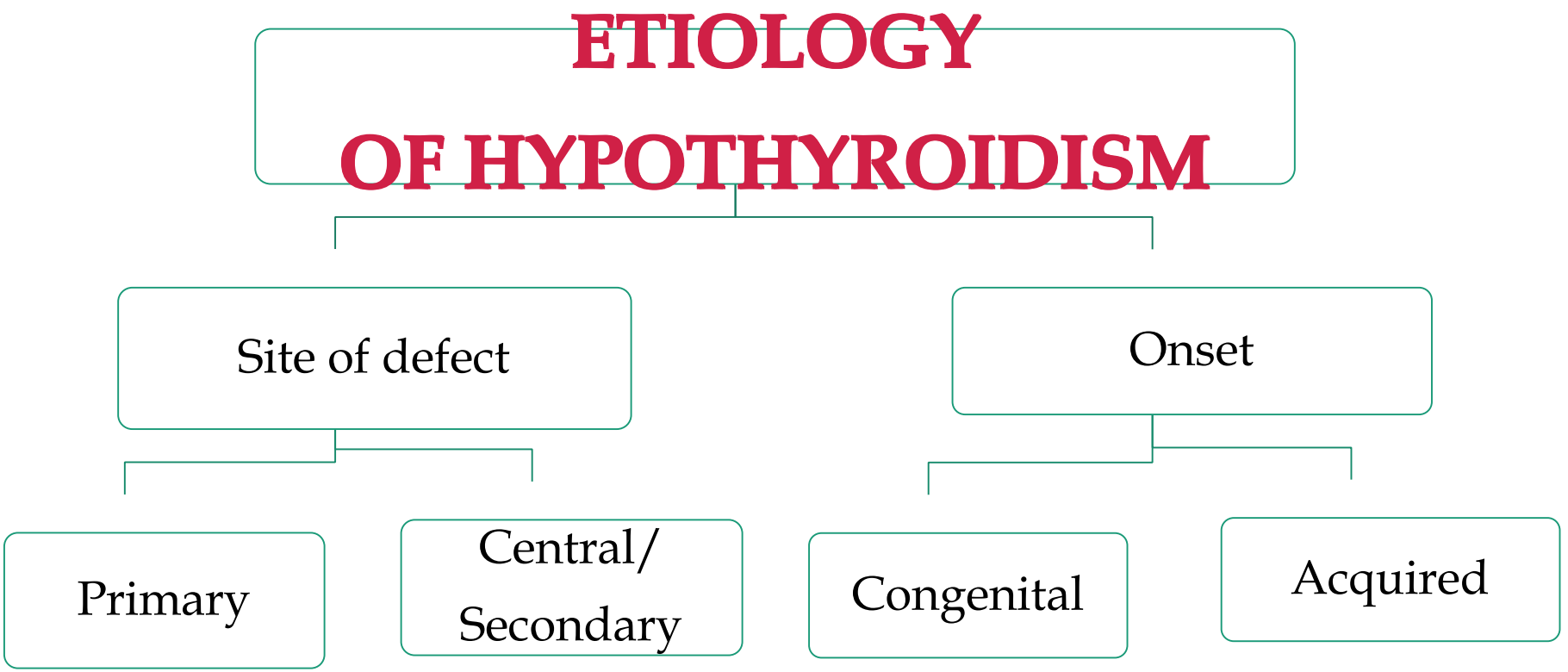
1. Binding of TSH to follicular cell TSH receptor.
2. Cyclic AMP activation.
3. Iodide trapping by thyroid follicular cells by Pendrin transporter
4. Oxidation and organification of iodide
5. Iodine combines with tyrosine to form MIT and DIT
6. Coupling of MIT and DIT to form T3, T4. Hormones are stored as colloid.
7. Hydrolysis of TG releases T3 , T4 into circulation.

Hypothyroidism

Hypothyroidism results from

- Deficient production of thyroid hormone due to the defects in the
  - hypothalamus or
  - pituitary gland or
  - thyroid gland

- Defect in thyroid hormone receptor activity . (Defect in peripheral sensitivity to thyroxin.)


ETIOLOGY
OF HYPOTHYROIDISM
Site of defect
Onset
Primary
Central/
Secondary
Congenital
Acquired

Hypothyroidism

When symptoms appear after a period of apparently normal thyroid function

1.the disorder may be truly “acquired” or

2.May appear so in some congenital defects in which the manifestation of the deficiency is delayed.

The term cretinism, although often used synonymously with endemic iodine deficiency and congenital hypothyroidism, is to be avoided.

Cretinism enotes congenital hypothyroidism in endemic Iodine deficiency areas.

CONGENITAL HYPOTHYROIDISM - EPIDEMIOLOGY

- Deficiency of thyroid hormone at birth
- 1 in 3000-4000 live births
- Sporadic(85%)
- Hereditary(15%)
- Female: Male (ratio) (2: 1)

One of the most common preventable cause of MENTAL RETARDATION in children.

PRIMARY HYPOTHYROIDISM

Defect in development (Dysgenesis-85%)	Aplasia, hypoplasia, ectopia
Defect in thyroid hormone synthesis (Dyshormogenesis-15%)	Iodide transport defect TSH unresponsiveness Organification defect Thyroid peroxidase defect Thyroglobulin synthesis defect Deiodination defect
Defect in thyroid hormone transport	
Iodine deficiency (endemic goiter)	Neurologic type Myxedematous type
Maternal antibodies	Thyrotropin receptor–blocking antibody
Maternal medications	Radioiodine, iodides, Propylthiouracil, methimazole, Amiodarone

CENTRAL (SECONDARY) HYPOTHYROIDISM

Defective gene protein	Inheritance	Consequences
PROP-1	Autosomal recessive	Deficiency of TSH, GH, Prolactin, LH, FSH, ACTH
PIT-1	Autosomal recessive Autosomal dominant	Combined deficiencies of growth hormone, prolactin, thyroid-stimulating hormone (TSH)
TSH	Autosomal recessive Mutation in TSH beta subunit gene	TSH deficiency
TTF-1 (TITF-1)	Autosomal dominant	Variable thyroid hypoplasia, choreoathetosis, pulmonary problems
TTF-2 (FOXE-1)	Autosomal recessive	Thyroid agenesis, choanal atresia, spiky hair
PAX-8	Autosomal dominant	Thyroid dysgenesis
TSH-receptor	Autosomal recessive	Resistance to TSH (e.g., type IA pseudohypoparathyroidism)

CENTRAL (SECONDARY) HYPOTHYROIDISM

Defective gene protein	Inheritance	Consequences
Na^+/I^- symporter	Autosomal recessive	Inability to transport iodide
Thyroid peroxidase	Autosomal recessive	Defective organification of iodide
Thyroglobulin	Autosomal recessive	Defective synthesis of thyroid hormone
Dehalogenase 1	Autosomal recessive	Loss of iodide reutilization
Pendrin	Autosomal recessive	Pendred Syndrome: Sensory neural deafness and partial organification defect of thyroid

CLINICAL FEATURES

- Most infants are asymptomatic at birth and symptoms appear gradually hence diagnosis is often delayed and neonatal screening tests are required.

- Birth weight & length - a big child or normal
- Head size - slightly increased.
- **Anterior fontanelle** - **wide**
- Posterior fontanel - patent.
- Cranial sutures - wide open
- **Macroglossia**

CLINICAL FEATURES:(contd)

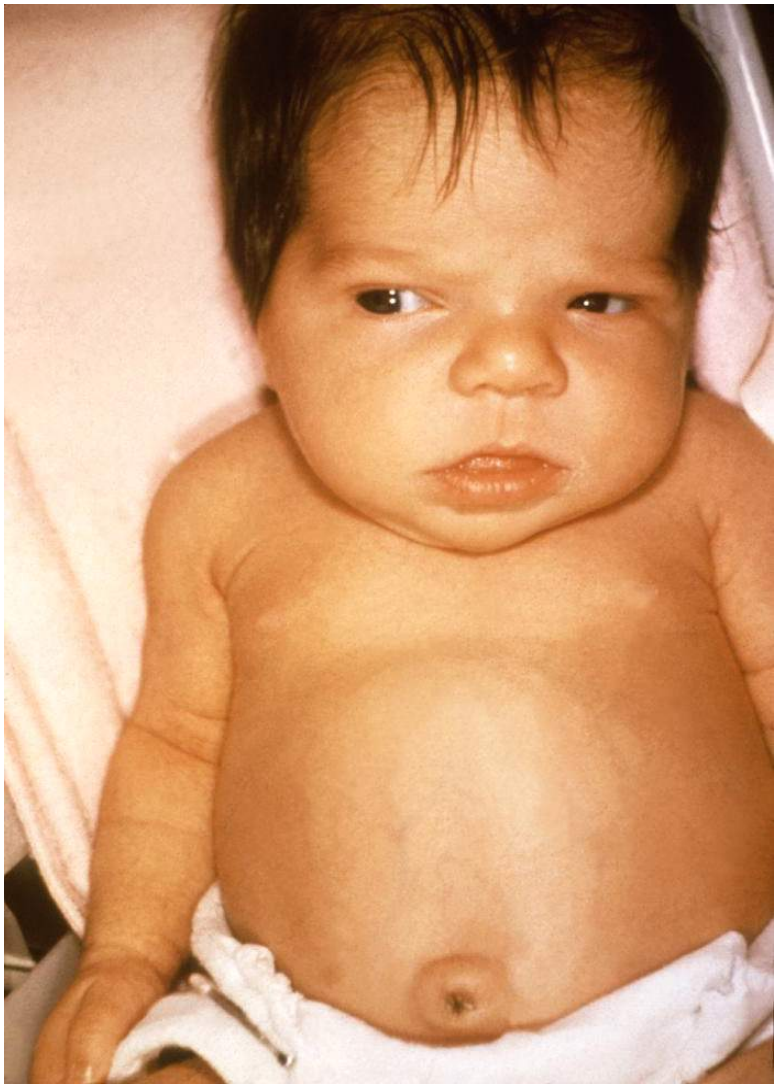
- Temperature - subnormal <than 35°c
- Pulse - bradycardia .
- Skin - dry & scaly, extremities cold and mottled
- Anemia - refractory to treatment
- Edema - genitals & extremities.
- Abdomen - large & **umbilical hernia , Constipation.**
- Heart - murmurs, cardiomegaly & asymptomatic pericardial effusion.

CLINICAL FEATURES:(contd)

- General disposition- cry little, sleep much, poor appetite
- **Feeding difficulties** - lack of interest, sluggishness, somnolence & choking spells.
- Respiratory difficulties -manifest as apneic episodes, noisy respirations and nasal obstruction
- Neck- Short
- Muscles - Flaccid, markedly **hypotonic**
- **Prolongation of physiological jaundice.**

CLINICAL FEATURES:(contd)

- Development - Retarded.
- Social smile - Delayed.
- Late in learning to sit and stand.
- Voice - hoarse & do not learn to talk.
- **Degree of physical & mental retardation increases with age**.
- Sexual maturation - Delayed or may not take place at all.



FULLY DEVELOPED CLINICAL PICTURE:

- CHARACTERISTIC COARSE FACIAL FEATURES:
- **Puffy face**
- Swollen eye lids.
- Anterior & posterior fontanelle widely open.
- Widely separated eyes
- Soft tissue myxedema
- Narrow palpebral fissures
- Broad nose with depressed bridge of nose
- Open mouth.
- Broad thick protuberant tongue.
- **Delayed Dentition .**
- Voice hoarse.
- Hair coarse,brittle,scanty

ASSOCIATED CONDITIONS

- Congenital Heart Diseases : ASD, VSD, PS
- Trisomy 18
- Trisomy 21
- Neural tube defects
- Metabolic disorders
- Turners Syndrome
- Hearing loss

MANAGEMENT - INVESTIGATIONS

➢Biochemical:

•TSH,freeT4,freeT3 levels

•Measurement of antithyroglobulin and antiperoxidase (acquired)

➢Radiological:

•USG neck

•X-ray's for Bone age

➢Nuclear:

•Radioactive $_{123}$I-sodium iodine uptake

•$_{99}$mTc-sodium pertechnetate

Investigations – Biochemical

- TSH — elevated > 100 mu/l (defect primarily in thyroid)
- Serum T4 or free T4 — low
- Serum T3 — low or normal
- Serum TG — Low (thyroid agenesis or defects of TG synthesis or secretion)
  Elevated (ectopic glands, inborn errors of thyroxin synthesis)
- TRH TEST : In primary hypothyroidism, administration of TRH produces prompt increase in TSH.
  In pituitary hypothyroidism , administration of TRH does not produce an increase in TSH.
  In hypothalamic hypothyroidism, administration of TRH produces a delayed increase in TSH.

NORMAL VALUES OF TSH AND T4 IN FULL TERM CHILDREN AND ADULTS:

AGE	TSH(mU\L)	FREE T4 (ng\dl)
1-4 DAYS	1.0 - 39.0	2.2 - 5.3
2-20 WKS	1.7 - 9.1	0.9 - 2.3
5-24 MTHS	0.8 - 8.2	0.8 - 1.8
2-7 YRS	0.7 - 5.7	1.0 - 2.1
8-20 YRS	0.7 - 5.7	0.8 - 1.9
21-45 YRS	0.4 - 4.2	0.9 - 2.5

DIAGNOSIS

- SUB CLINICAL HYPOTHYROIDISM--TSH-↑, Free T4-N
- PRIMARY HYPOTHROIDISM --TSH-↑, FREE T4↓
- CENTRAL HYPOTHYROIDISM --TSH-N/↓, FREE T4↓

X Ray films of bones in congenital hypothyroidism

Retardation of osseous development can be shown radiographically in about 60% of congenitally hypothyroid infant.

1.Absence of distal femoral epiphysis.

2 .Discrepancy b\w chronological age and osseous development in untreated patients.

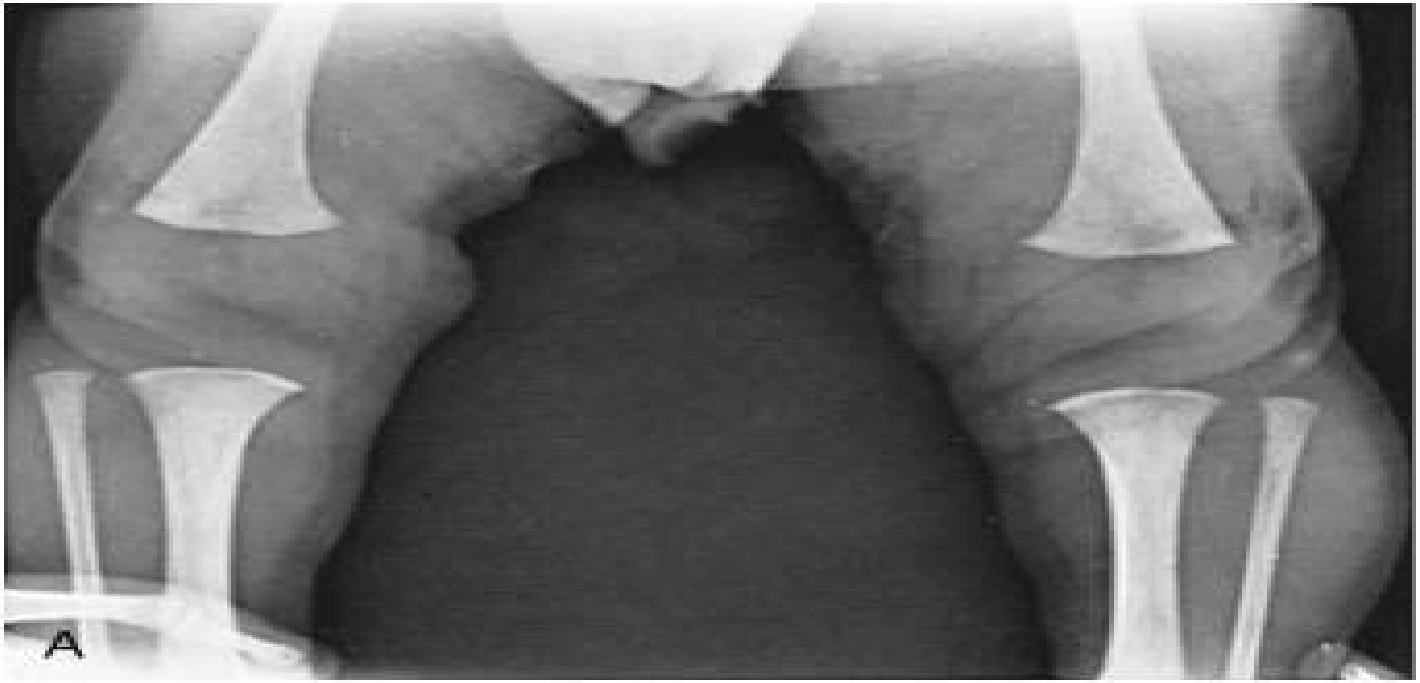
3 .Epiphyseal dysgenesis.

4. Beaking of 12th thoracic, 1st or 2nd lumbar vertebral column

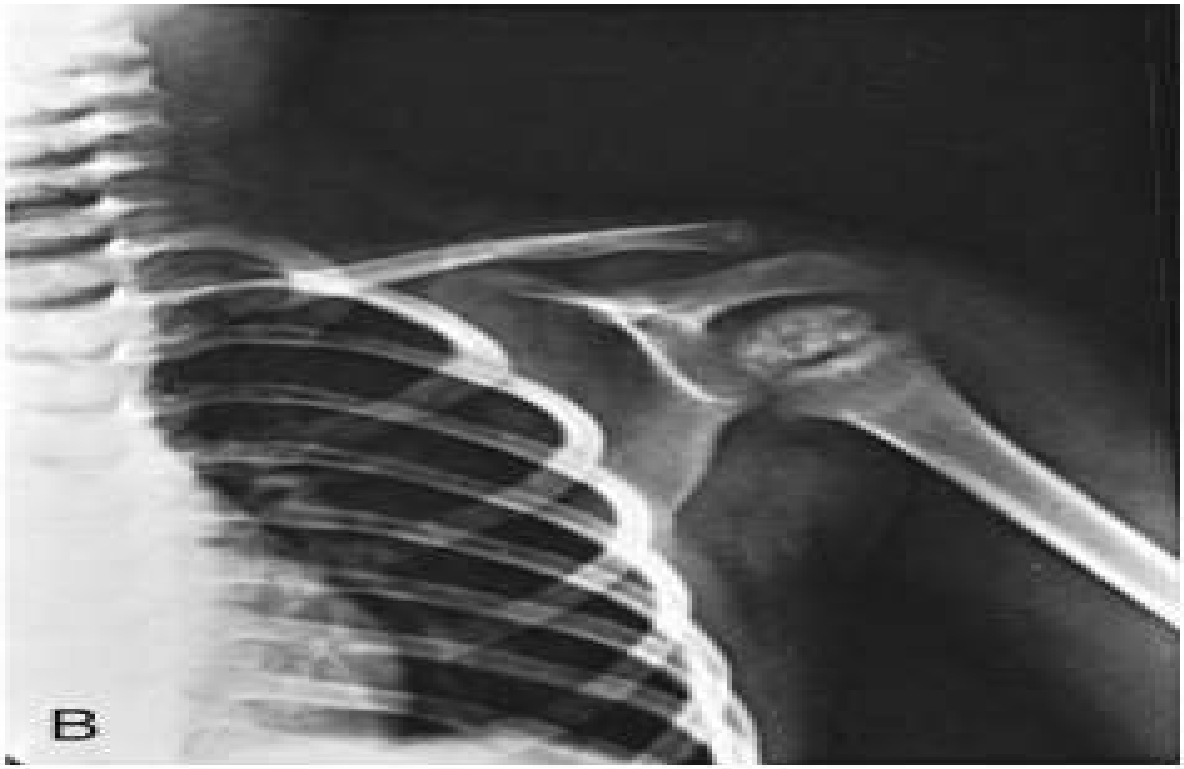
5. Shortening of long bones

Radiography

Distal femoral epiphysis normally present at birth , is absent in a 3mo old child



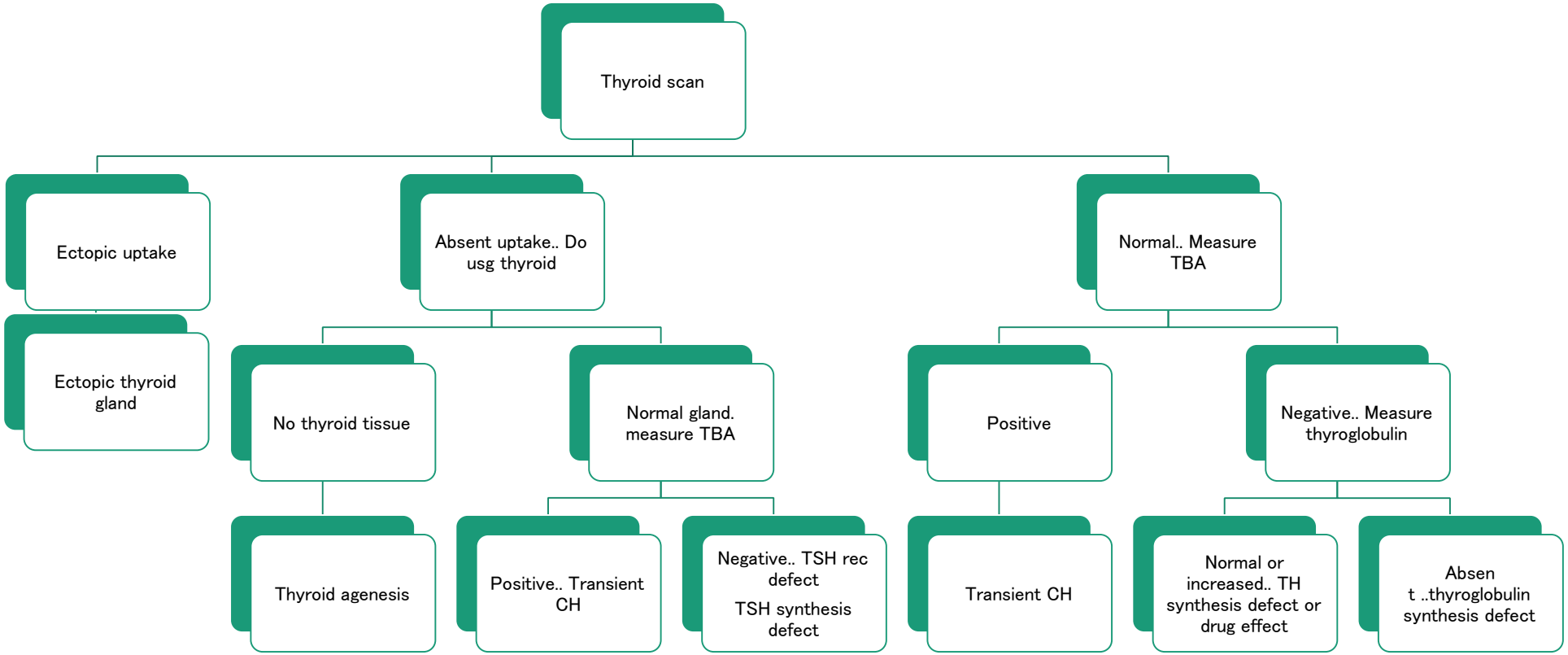
Epiphyseal dysgenesis in the head of humerus of a 9 yr old child



Diagnosis

- Following are the markedly improved direct tests for thyroid function.
- **Thyroid Scan / RAIU**
- when the thyroid tissue is in question (ectopic/ agenesis)
- Technitium pertechnetate $_{99m}$Tc or $_{123}$I is a high quality scintigram with low radiation exposure. (trapped but not organified; half life-6 hrs)
  - low in dysgenesis
  - elevated in iodine deficiency & most cases of inborn errors of thyroxine synthesis

- **Thyroid USG:**
- Useful to determine the location, size and shape of the thyroid gland


Thyroid scan
Ectopic uptake
Ectopic thyroid gland
Absent uptake.. Do usg thyroid
No thyroid tissue
Thyroid agenesis
Normal gland. measure TBA
Positive.. Transient CH
Negative.. TSH rec defect
TSH synthesis defect
Normal.. Measure TBA
Positive
Transient CH
Negative.. Measure thyroglobulin
Normal or increased.. TH synthesis defect or drug effect
Absen t ..thyroglobulin synthesis defect

Treatment

- **TREATMENT OF CHOICE : T.SODIUM-L-THYROXINE**

	Dose microg/kg/day
0 to 3 months	10 to 15
3 to 12 months	6 to 10
1 to 3 Yrs	4 to 6
3 to 10 Yrs	3 to 5
10 to 16 yrs	2 to 4
Adults	2

- T4 & TSH monitored at recommended intervals

Side Effects of Sodium-levo-Thyroxine

- Dose related
- Over treatment may risk craniosynostosis
- Temperament problems
- Changes in behaviour and activity
- Developmental or neurologic deficits
- Osteoporosis may result from excessive dosage

Follow up

- **Monitor TSH and FREE T4:**
- Two and four weeks after starting treatment, then:
- Every one to two months until 1 year of age
- Every two to three months until 3 years of age, and
- Every three to 12 months until growth is completed.

Prognosis

- Early diagnosis and adequate treatment from first week of life result in normal linear growth & intelligence.
- Severely affected infants have reduced IQ and other neuropsychologic sequelae.
- 20% children may have neuro-sensory hearing deficit.
- Without treatment affected infants become profoundly mentally deficient dwarfs.

Prognosis (contd)

- Delay in diagnosis, failure to initially correct hypothyroxinemia rapidly, inadequate treatment & poor compliance in first 2-3 yrs of life result in variable degree of brain damage.

- Onset of hypothyroidism after 2 yrs of age, normal development is much better even if diagnosis & treatment have been delayed.

- Thus indicating importance of thyroid hormone in the rapidly growing brain of infant.

Prevention

- NEONATAL SCREENING

- **Time of blood sampling: 3-5 days of age**
- All abnormal results need to be investigated by repeating the test, further tests

- IODINATED SALT

Neonatal Screening

- At the time of parturition the neonate must rapidly convert from the state of predominant thyroid hormone inactivation to a state of relative thyroidal hyperactivity.

- During the first hours of birth there is an abrupt twofold to sixfold increase in circulating T4 and T3 levels.

- This is caused by an increase in TRH and TSH.

- This surge starts at 30 min, peaks at about 24 hrs post partum and plateaus at about 48 hrs of life T4 levels **decline by 3-5 days after birth.**

Neonatal Screening

- All abnormal results need to be investigated by further testing.

- Screening programs use either percentile based cut-offs (e.g, T4 below 10th centile or TSH above 90th centile or absolute cut-offs such as T4 < 6.5 ug/dL and TSH > 20mu/L.

- Positive screening test on filter paper sample should always be confirmed by a venous sample (using age appropriate cut-offs).

Neonatal Screening (contd)

In the absence of universal screening, the newborns with the following indications should be screened:

- Family history of CH
- History of thyroid disease or antithyroid medicine intake in mother
- Presence of other conditions like Down's syndrome, trisomy 18, neural tube defects, congenital heart disease, metabolic disorders, familial autoimmune disorders and Pierre- Robbins syndrome which are associated with higher prevalence of CH
- Clinical suspicion - QUEBEC SCORE

NEONATAL SCREENING(CONT)

Clinical Scoring – Quebec Score

- ❑Feeding problem - 1
- ❑constipation - 1
- ❑inactivity - 1
- ❑hypothermia - 1
- ❑macroglossia - 1
- ❑patent post –fontanelle - 1.5
- ❑typical facies - 3
- ❑umbilical hernia -1
- ❑skin mottling -1
- ❑dry skin -1.5
- ❑total score 1

>4/13 SUSPECT C.H

THANK-YOU