THYROID DISORDERS

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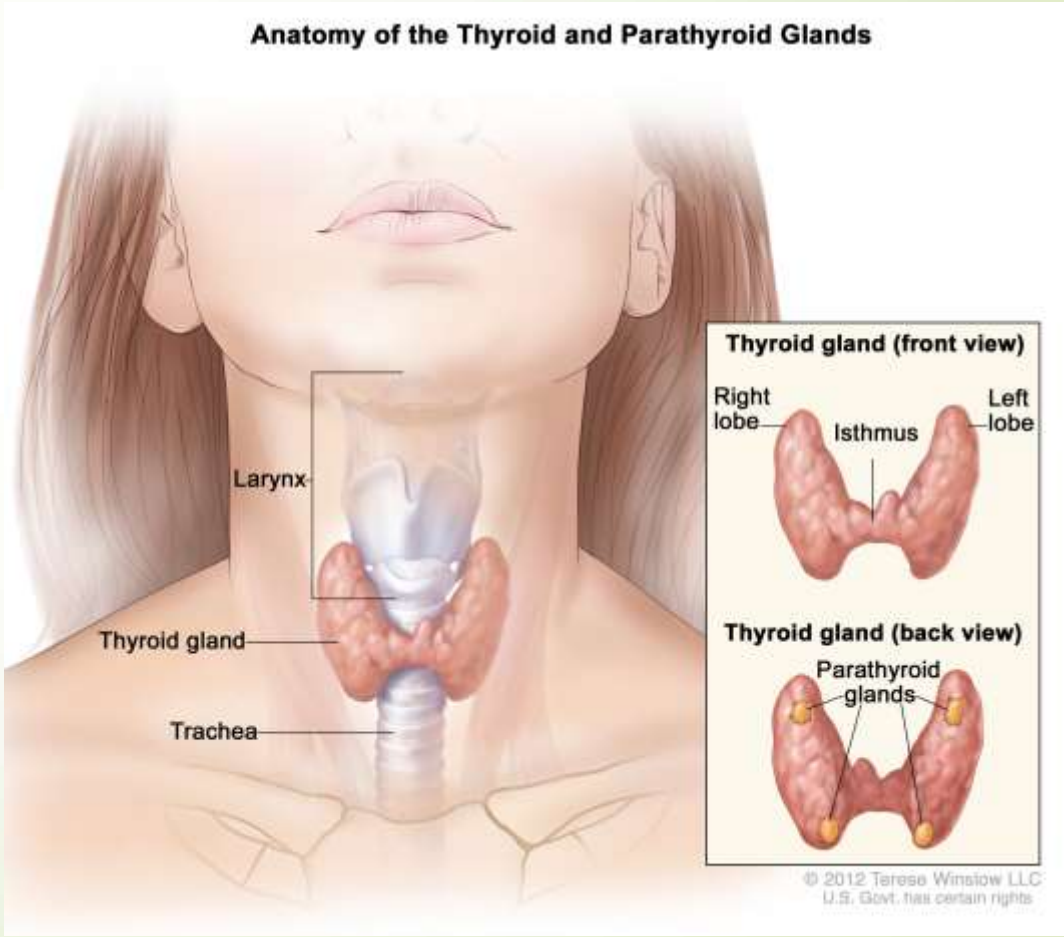


Thyroid development

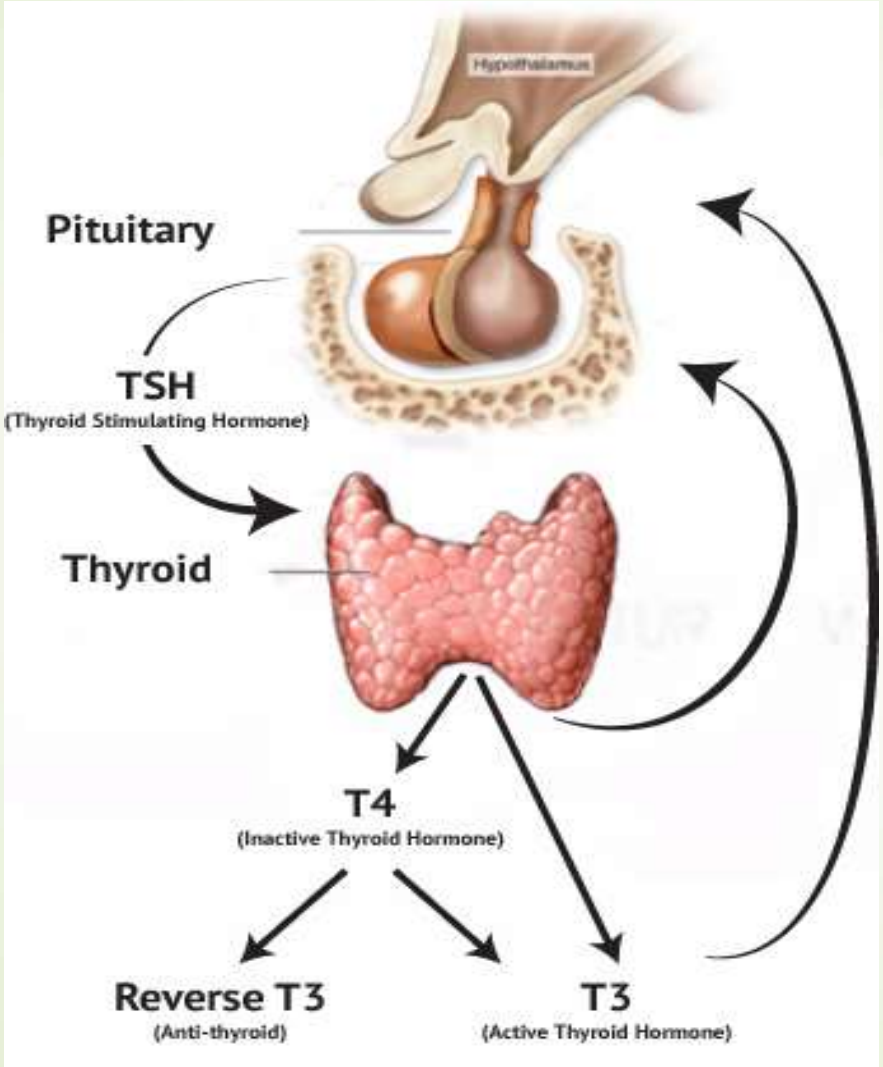
- Fetal thyroid bilobed shape 7 weeks
- T4 T3 secretion 12 weeks
- TRH thyrotropin releasing hormone 6-8 wk
- TSH secretion 12 weeks

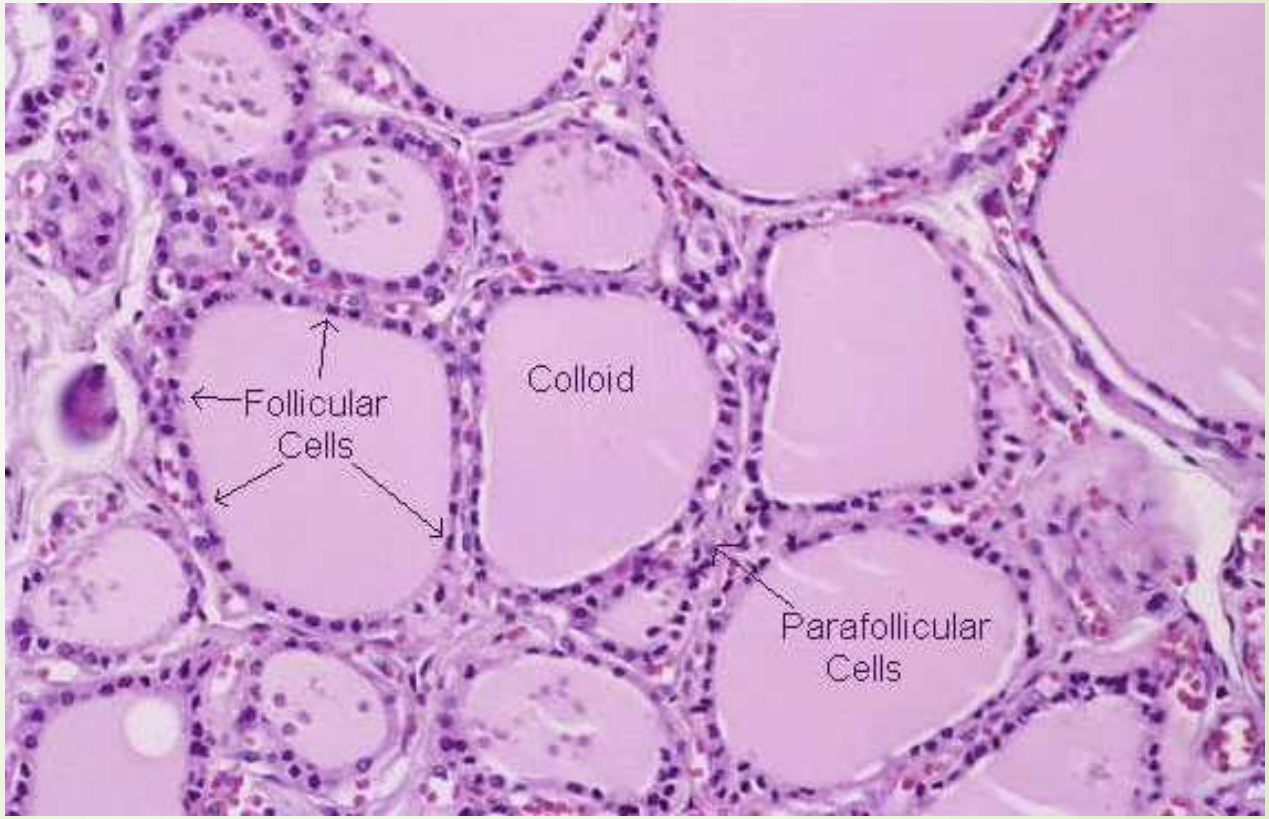
Physiology

- TRH→ TSH (Thyrotropin)→ T4 and some T3
- 80% Of T3 is produced by peripheral deiodination of T4
- T3 is the active form while T4 is more of a prohormone
- T4 binds very tightly to TBG and to albumin

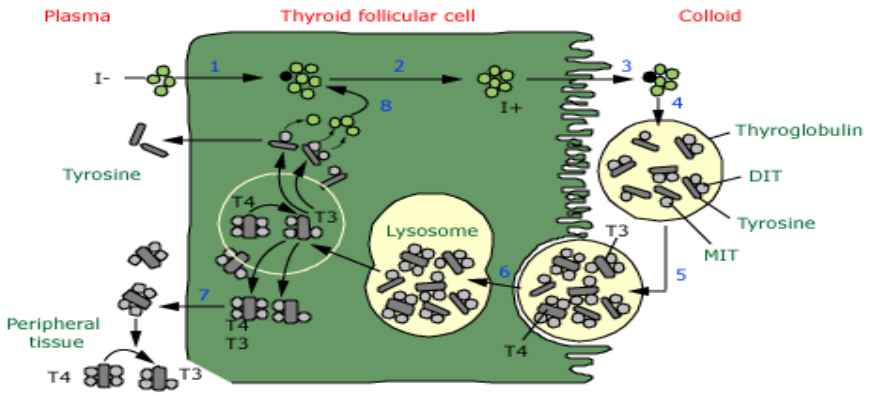
Cont. physiology

- T3 also binds to these proteins but not as strongly
- Only a very **small** fraction of the total T4 and total T3 is **unbound** and **active**
- Total T4=bound + free(unbound)


Hypothalamus
Pituitary
TSH
(Thyroid Stimulating Hormone)
Thyroid
T4
(Inactive Thyroid Hormone)
Reverse T3
(Anti-thyroid)
T3
(Active Thyroid Hormone)


Follicular
Cells
Colloid
Parafollicular
Cells

Thyroid hormone biosynthesis



Thyroid hormone synthesis includes the following steps: (1) iodide (I^-) trapped by the thyroid follicular cells; (2) diffusion of iodide to the apex of the cells; (3) transport of iodide into the colloid; (4) oxidation of inorganic iodide to iodine and incorporation of iodine into tyrosine residues within thyroglobulin molecules in the colloid; (5) combination of two DIT molecules to form tetraiodothyronine (T4) or of MIT with DIT to form T3; (6) uptake of thyroglobulin from the colloid into the follicular cell by endocytosis, fusion of the thyroglobulin with a lysosome, and proteolysis and release of T4, T3, DIT, and MIT; (7) release of T4 and T3 into the circulation; and (8) deiodination of DIT and MIT to yield tyrosine. T3 is also formed from monodeiodination of T4 in the thyroid and in peripheral tissues.

T4: thyroxine; T3: triiodothyronine; DIT: diiodotyrosine; MIT: monoiodotyrosine.

Modified from: Scientific American Medicine, Scientific American, New York, 1995.

Thyroid changes at birth

- At birth, there is a surge of TSH that peaks by 12 hrs of age
- Followed by a rise in T4 and T3 levels, which peak during the first day of life and then slowly fall
- Important for interpretation of newborn screening tests
- Prematures and sick babies have less of a TSH surge

Actions of the thyroid hormones

- Increase the oxidative metabolism:

-↑ oxygen consumption -↑BMR -↑glucose metabolism -↑ fat metabolism.

- Promote growth and development.
- Essential for normal myelination and development of CNS.
- Augmentation of cardiac function.
- Important for normal reproductive function

Interpretation of thyroid function test

- High TSH➔ look for T4:
  - low➔ primary hypothyroidism
  - normal➔ subclinical hypothyroidism
  - high➔ pituitary hyperthyroidism
- Low TSH ➔look for T4:
  - low➔ pituitary hypothyroidism
  - normal➔ subclinical hyperthyroidism
  - high➔ thyrotoxicosis

Disorders of the thyroid gland

- Hypothyroidism

Congenital or acquired

Primary vs. central

Transient vs. permanent

- Hyperthyroidism

Congenital or acquired

Primary vs. central

Transient vs. permanent

- Thyroid storm

Hypothyroidism

Congenital hypothyroidism

- is one of the most common preventable causes of intellectual disability (mental retardation)
- Mostly it is primary
- Incidence 1 in 4000
- F>M (2:1)

Congenital hypothyroidism(cretinism)

- **cretinism is defined**
  as arrested physical and mental development with dystrophy of bones and soft tissues, due to congenital lack of thyroid secretion.

- Permanent vs. transient(eg.iodine exposure)
- Primary vs. secondary (central)
- Goiterous vs. nongoiterous

- Risk factors:

1. Prematurity
2. Multiple gestations
3. Babies of old age mothers
4. Asians and hispanics
5. Down syndrome

Etiology

1. Dysgenesis 90% (no palpable tissue, no goiter)

- Aplasia(no remnants of thyroid tissue) in one third
- Hypoplasia or ectopic location in two thirds

- Factors in normal thyroid migration and development are TTF-1 TTF-2 and PAX-8
- USUALLY sporadic

Cont. etiology

2. Thyrotropin receptor-blocking antibody(TRBAb)

- rare, lead to transient congenital hypothyoidism
- due to transplacental passage of maternal Abs
- remission in 3 months

Etiology (cont)

3) Dyshormogenesis (disorder of intrathyroid metabolism)

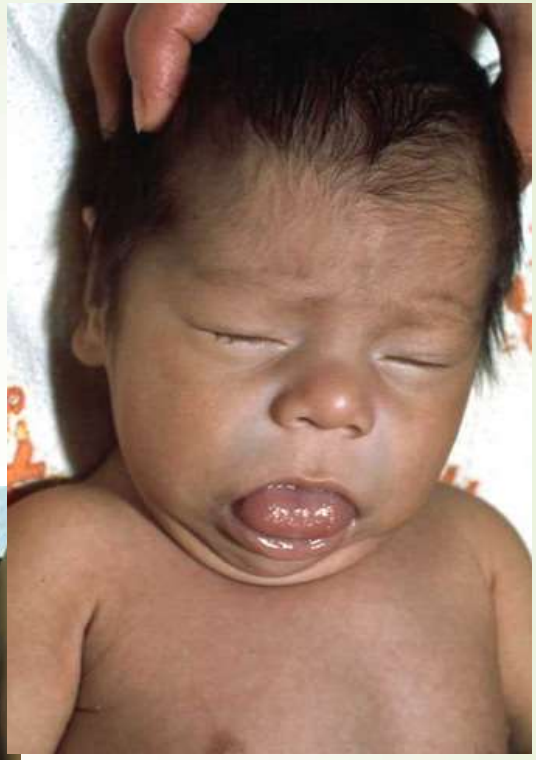
- goiterous (almost always)
- rare 1in 30000
- inborn errors of metabolism (inherited) or antithyroid drugs during pregnancy

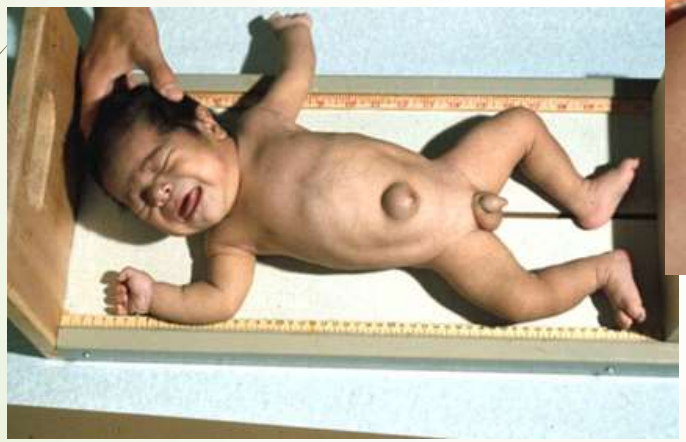
Clinical manifestations

- Most infants are asymptomatic at birth. Why?
- Birth weight and length are normal, but head size may be slightly increased.
- Symptoms appears weeks or months later
- Neonatal screening is crucial for early diagnosis and initiation of replacement RX
- Gestation greater than 42 wks
- Birth wt greater than 4 kg
- Hypothermia
- acrocyanosis

Clinical manifestations:

- Respiratory distress
- Large posterior fontanelle
- Abdominal distention
- Lethargy and poor feeding
- Prolonged Jaundice (may be the earliest sign)
- edema
- Umbilical hernia
- Mottled skin
- Constipation
- Dry skin
- Hoarse cry(cry little.sleep much,poor appetite)





Clinical manifestations:

- By age 3-6months the clinical picture is fully developed
- Growth is stunted,extremities are short. Head size normal or increased
- Open posterior fontanelle
- The mouth is kept open.and large tongue protruding
- Dention is delayed
- Neck is short and thick

Clinical manifestations:

- Broad Hands , short fingers
- Skin is dry and scaly little perspiration
- Myxedema of the eyelids, dorsum of hands and ext genitalia
- Carotenemia :yellow skin white sclera
- Scalp is thickened hair is coarse brittle and scanty
- Low hair line

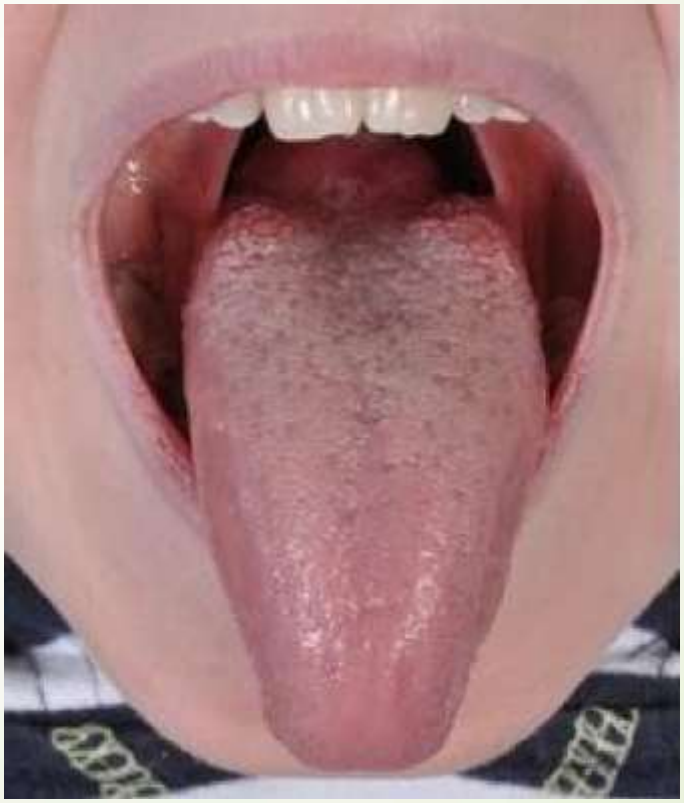
Clinical manifestations:

- Bone age delay
- Brain maturation

  thyroid hormone is essential for bone and brain maturation
- Development is retarded

- Muscles hypotonia

A lingual thyroid in an eight year old girl, who was asymptomatic yet aware of the lump's presence.



Diagnosis

- Sceening programs allow early detection

  T3 T4 LOW

  TSH HIGH more than 100 mU/l
- Serum level of prolactin are elevated
- Delay in osseous development(distal femoral epiphysis absence) ---epiphysial dysgenesis
- Thyroid u/s
- thyroglobulin

Diagnosis

- Skull x ray large fontanelle,wide sutures,wormian bones, sella turcica large and round
- THYROID SCAN detect presence or absence of thyroid tissue
- ECG low voltage P,T wave QRS complex

screening strategies

Three major screening strategies have evolved:

1. **Initial blood thyroxine (T4) assay, with follow-up thyrotropin (TSH) assay if the blood T4 value is below a certain concentration (usually less than the 10th percentile)**
2. **Initial blood TSH assay**
3. **Simultaneous T4 and TSH assay**

Approach one vs. two

- Either approach detects the majority of infants with **congenital primary hypothyroidism**
- Infants with a delayed rise in blood TSH concentration and those with **central hypothyroidism** most commonly are detected by the initial T4/follow-up TSH assay method
- infants with **subclinical hypothyroidism** (high blood TSH, normal blood T4) most commonly are detected by TSH testing
- Most newborn screening programs worldwide (even those that employ primary T4 testing) do not detect cases of congenital central hypothyroidism because their T4 level is above the screening cutoff. *clinicians should not be falsely reassured by a normal screening T4 result*.

Cont. screening

- Screening with multiple tests (eg, T4 and TSH, or T4 and TSH and thyroxine-binding globulin [TBG]) has been suggested as a way to improve detection of both **primary and central hypothyroidism**
- However, the improved detection rate is associated with an increased number of false-positive screens which may lead to unnecessary parental anxiety as well as a potential rise in overall cost.

Treatment

- Sodium Thyroxine T4
- New born 10—15 ug/kg not mix with soy protein or iron
- Child hood 3-5 ug/kg
- Adults only 2 ug/kg

Prognosis

- There is an inverse relationship between age at clinical diagnosis and treatment initiation and intelligence quotient (IQ) later in life, so that the longer the condition goes undetected, the lower the IQ.

- RX initiated within first month prognosis is excellent
- After 6 months bad for intellectual development
- Growth improve even in late cases
- Onset after 2 years out look for normal development is much better

QUESTION

- Does breastfeeding adequate to protect an infant with congenital hypothyroidism?
- Does it affect neonatal thyroid screening tests?

Acquired hypothyroidism

- Etiology

1. Lymphocytic thyroiditis most common
2. Autoimmune polyglandular syndome
3. Down ,turner,klinfelter syndromes
4. Subtotal thyroidectomy
5. Histiocytic infiltration
6. Irradiation
7. Amiodarone

Hypothyroidism
Clinical manifestations:

- Deceleration of growth
- Myxedematous change of skin
- Constipation
- Cold intolerance
- Decreased energy and concentration
- Increase need for sleep
- Osseous maturation is delayed
- Delay or precocious puberty

hypothyroidism

First year of treatment

Deterioration school work

Poor sleeping habit

Restlesness

Short attention span

Behavioral problems

Hashimoto thyroiditis

- Also known autoimmune or lymphocytic
- Most Common cause of goiter and hypothroidism in older children and adolsecent and also hypo without goiter
- Incidence 1% school children
- Positive F H in 25 to 35% suggesting genetic predisposition
- Etiology: autoimmune process lymphocytic

infiltration of thyroid

Hashimoto

Etiology

- Lymphocytic infiltration T cells 60%

  Bcells 30%
- Thyroid antiperoxidase Ab [TPOAb](antimicrosomal) in 90% of cases
- Antithyroglobulin more common in adults.

Hashimoto

- 4-7 times more in girls
- Onset insidious after 6 yr peak--- adolescene
- The most common presentation growth retardation and goiter
- Goiter diffuse firm non tender
- Euthyroid hypothyroid hyperthyroid(rare) most are Euthyroid
- Ocassionally may co-exist with graves
- Ophthalmopathy may ocur

Hashimoto

- Clinical course
- Variable
- Goiter smaller disappear or persist
- Euthyroid mostly continue same
- Familial cluster incidence in sibs or parents of affected children 25%
- Autoantibodies are inherited as AD

Hashimoto

Associated auto immune diseases:

DM1

Adrenal inssufficiency

hypoparathyroidism

Hashimoto

Autoimmune Polyglandular syndrome type 1

hypoparathyroidism

addison disease

mucocutaneous cadidiasis

often

hypothyroidism----10%

Autoimmune Polyglandular syndrome type11

Addison disease
DM1 and frequently
hypothyroidism

Hashimoto

- Other assosciation
  - Pernicious anemia
  - Vitiligo
  - Alopecia
  - Congenital rubella
- Predisposing factors
  - Trisomy 21
  - Turner syndrome

Diagnosis of Hashimoto thyroiditis

1. **T3 T4** often normal **TSH** slight elevation
2. **Antithyroid peroxidase (**antimicrosomal**)**
3. **Antithyroglobulin antibodies**
4. **Thyroid U/S:** scattered hypoechogenicity
5. **Thyroid scan** 50% irregular and patchy distribution
6. Definitive Dx: by **biopsy** of thyroid

NOTE :Neither biopsy nor thyroid scan OR U/S is indicated

Treatment of Hashimoto thyroiditis

- Replacement Rx with **levothyroxine** sufficient to depress TSH to normal level in case of **hypothyroidism**
- **Euthyroid** cases follow up 6-12 months to check T3 T4
- **Goiter** with normal TSH, usually no treatment, contoversial
- **Subclinical hypothyroidism**: controversy

- Treated patients Periodic re-evaluation , may be self limited
- Untreated patients periodic re-evaluation

Hyperthyroidism

Hyperthyroidisim

- Result from excessive secretion of thyroid hormone
- With few exceptions its due to **GRAVES** (diffuse thyroid hyperplasia)
  - Other causes
- Mc cune-albright
- Toxic uninodular goiter (plummer disease)
- TSH secreting pituitary tumors

GRAVES DISEASE

- ETIOLOGY
- Enlargement of thymus,spleen,LN,infiltration thyroid gland retro orbital tissue with lymphocytes plasma cells, peripheral lymphocytosis
- Plasma cells produce thyrotropin receptor-stimulating antibodies(**TRSAb**)
- **TRBAb** thyrotropin receptor- blocking antibodies also produced

Etiology cont GRAVES DISEASE

- In whites associated HLA- B8 HLA- DR3
- Other associations

Addison

DM1

myasthenia graves

celiac disease

SLE

RH arthritis

vitiligo ITP Pernicious anemia

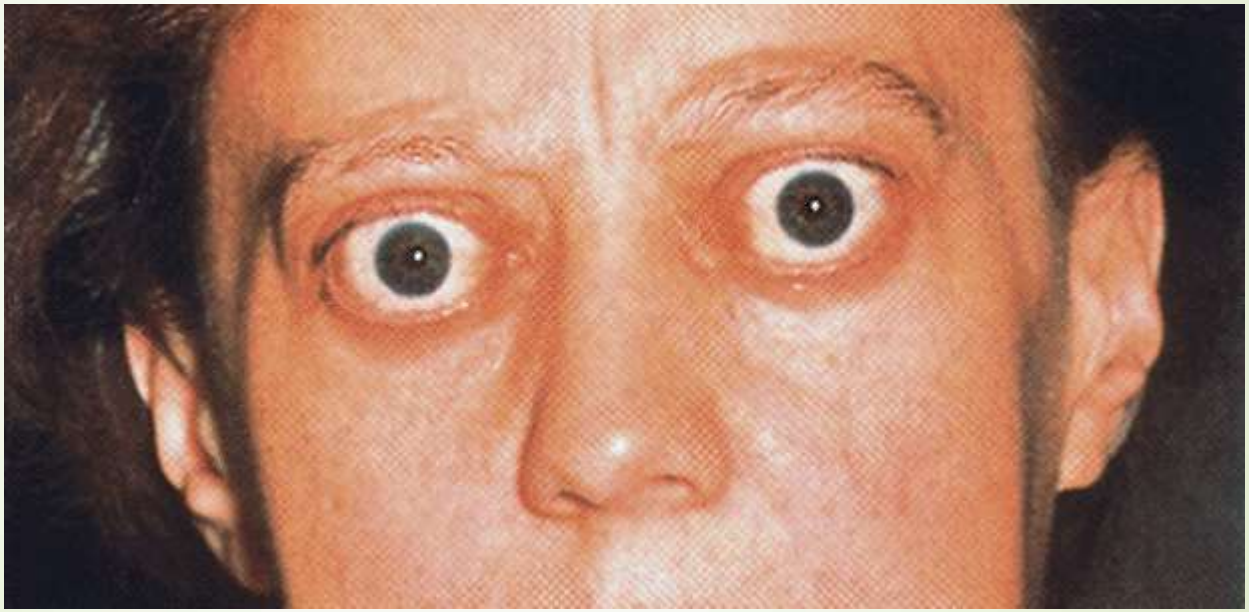
Clinical manifestations of GRAVES DISEASE

- 5% of patient less than 15 years
- 6 wk----2yrs if mother HX hyperthyoidism
- 5 times higher in girls
- Onset gradual
- interval from onset to symptoms 6-12 months
- Earliest sign emotional disturbances irritable excitable cry hyperactive
- School work deteriorate short attention span

Clinical manifestations cont
GRAVES DISEASE

- Tremor
- Voracious appetite with loss of weight
- Goiter found in most pt
- Exophthalmos noticeable but mild
- lid lag
- Skin smooth and flushed, excessive sweeting
- Muscular weakness
- Tachycardia palpitations dyspnea cardiomegally
- Atrial fibrillation rare complication

Note: Eye manifestations are much less common in children than adults



Clinical manifestations cont GRAVES DISEASE

- Mitral regurgitation
- Systolic B/P and pulse increase90
- Advanced skeletal maturation and craniosynostosis (neonatal graves)

Thyroid crisis (storm)

Acute onset

Hyperthermia

Severe tachycardia

Restlesness

Delirium coma death

Lab finding

- T4 T3 FREE T3 T4 are elevated
- TSH are suppressed
- Thyroid peroxidase antibodies present
- TRSAb are present in newly diagnosed cases its disappearance mean remission

Differential diagnosis (cont)

- If precocious puberty ,café au lait spot and polyostotic fibrous dysplasia **McCune-albright**
- Generalized thyroid hormone unresponsiveness **(Thyroxine resistance)**
- High level T3 but levels TSH elevated or normal
- **Exogenous** thyroid hormone, T4 TSH same as Graves but thyroglobulin is very low.

Treatment

- Medical therapy
- Radio-active iodine ablation
- Subtotal thyroidectomy

Medical therapy (antithyroid drugs)

1. Propylthiouracil(PTU)
2. Methimazol

- Inhibit incorporation of trapped inorganic iodide into organic compound
- Suppress level of TRSAbs by direct effect
- Additional effect of PTU: inhibits the conversion of T4→T3

PTU VS. Methimazole,Carbimazole

- Methimazole
- PTU Preferred in pregnancy and lactating mothers,

Not preferred in pediatrics due its hepatotoxicity effects

Toxic reactions occur with both

- Transient leukopenia
- Transient urticarial rash

Severe reactions

- Agranulocytosis
- Hepatitis, hepatic failure(PTU mainly)
- SLE like syndrome

Relapse

- Appears within 3 months and almost always within 6 months

Beta adrenergic blocking agent

- Propranolol
- 0.5—2mg/kg for catecolamine effect like:
  - tachycardia
  - tremor
  - sweating
  - Lid lag

Surgery and Radioiodine

- **Indications** :When medical either not possible or failed

Subtotal thyroidectomy complication include

- hypoparathyroidism
- paralysis vocal cord
- recurrence --- rare

Radioactive iodine Ablation

- Effective
- Relatively safe
- One dose cure 88% some needs second or third dose
- Complications : hypothyroidism

  oncogenesis

Congenital hyperthroidism (congenital thyrotoxicosis)

- Onset prenatally
- Present at birth
- Noticed few days later
- Mothers have active or in remission Graves
- Transplacental passage of TRSAb

Congenital hyperthroidism

- Only 2% infants born to mothers with HX of Graves
- High levels of TRSAb in mothers predict occurrence
- Fetal tachycardia and goiter allow prenatal DX
- Remits spontaneouslly within 6-12 wks but occasionally persists

Congenital hyperthroidism

Clinical manifestations

- Premature or IUGR
- Most have goiter
- Restless,irritable,hyperactive,anxious.alert
- Microcephaly
- Eyes open widely exophthalmic.

Congenital hyperthroidism

- Tachycardia .tachypnia,high Temp
- Good appetite wt loss
- Jaundice ,
- hepatosplenomegaly
- Cardiac decompensation hypertension
- May die if RX not started promptly

Congenital hyperthroidism

- T3 T4 elevated
- TSH suppressed
- Advanced bone age
- Frontal bossing and craniosynostosis
- PROGNOSIS for IQ is guarded

Treatment of Congenital hyperthroidism

- Carbimazole
- Propranolol 2mg/kg/d po TID
- Lugol solution 1 drop /8 hrs
- IVF and STEROIDS in severe cases
- Digoxin for heart failure

Thank you