Thyroid Disorders
In Children

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Objectives

1) Hypothyroidism

- At the end of the lecture, medical student will be able to:
  - Knowledge on anatomy, physiology of the thyroid gland and thyroid hormone biosynthesis
  - Description of the hypothalamic-pituitary regulation of Thyroid Gland
  - Enumerate various cause of primary, Secondary and tertiary hypothyroidism including congenital and acquired hypothyroidism
  - Description of the clinical features of congenital and acquired hypothyroidism
  - Knowledge on how to investigate and expected laboratory findings
  - Knowledge on importance of neonatal screening program for congenital hypothyroidism
Objectives

2) Hyperthyroidism

• At the end of the lecture, medical student will be able to:
  – Enumerate various causes of thyrotoxicosis including neonatal form
  – Description on Pathophysiology of thyrotoxicosis and association with other autoimmune endocrinopathy
  – Description of clinical presentation of thyrotoxicosis
  – Enumerate various causes of thyrotoxicosis.
  – Description clinical manifestation of eye disease in Grave’s thyrotoxicosis.
  – Knowledge on different laboratory and radiological investigation tools in cases of thyrotoxicosis
Anatomy

- Over Trachea
- Two Lobes connected together by an isthmus
- 15 to 20 g
Thyroid gland

- Thyroid gland derives from the floor of embryonic pharynx
- Begins to develop around 4 weeks of gestation
- Moves down the neck while forming its characteristic bilobular structure
- Thyroid development is largely completed between 10-20 weeks of gestation
- Thyroid gland size increases gradually by 1g/year until age of 15 years where it achieves adult size (15-25 g)
Sites of normal & ectopic thyroid tissue

Fig. 13.6 Sites of normal and ectopic thyroid tissue along the line of the thyroglossal duct. Remnants of the duct may persist as isolated nests of functioning thyroid tissue, for example as a lingual thyroid, a pyramidal lobe or as simple thyroglossal cysts.
Thyroid gland

- Thyroid gland is composed over a million cluster of follicles.
- Follicles are spherical & consists of epithelial cells surrounding a central mass (colloid).
- Thyroglobulin is storage room.
- Two main hormones:
  - Tetraiodothyronine (Thyroxin)
  - Triiodothyronine
FUNCTIONAL UNIT IS THE FOLLICLE
Thyroid gland

- Thyroid gland normally secretes mainly T4
- 70% of T3 derived from T4 in peripheral tissues
- T4 is converted to T3 by 5-deiodinase enzyme
- Both T4 and T3 are in bound form (TBG, prealbumin and albumin)
- Only 0.025% of T4 and 0.35% of T3 are free
- Free hormone concentration best correlates with thyroid status
- T4 production is 5-6 µg/kg/day in infancy with gradual decrement to 1.5 µg/kg/day in adult
Thyroid Regulation

Somatostatin, Glucocorticoid

Dopamine
Thyroid hormone synthesis

1) Iodide pump

• Rate-limiting step in thyroid hormone synthesis which needs energy
• Follicles have in their basement membrane an iodide trapping mechanism which pumps dietary I⁻ into the cell
• Normal thyroid: serum iodine is 30-40:1
  – Iodide uptake enhancers:
    • TSH
    • Iodine deficiency
    • TSH receptors antibody
  – Iodide uptake inhibitors
    • Iodide ion
    • Drugs
      – Digoxin
      – Thiocynate
      – perchlorate
Thyroid hormone synthesis

2) Iodide oxidation to iodine and Organification

• Inside the cells, iodide is oxidized by peroxidase system to more reactive iodine

• Iodine immediately reacts with tyrosine residue on a thyroid glycoprotein called “thyroglobulin” to form:
  – T1= mono-iodotyrosyl thyroglobulin
  – T2= di-iodotyrosyl thyroglobulin

• Both processes are catalyzed by thyroid peroxidase enzyme
3) Coupling
• T1 & T2 couple together to form T3 & T4
• MIT + DIT = T3 (Tri-iodothyronine)
• DIT + DIT = T4 (Thyroxin)
• All attached to thyroglobulin and stored in the colloid Thyrogblobulin molecule
• This process is stimulated by TSH
Production of Thyroid Hormones

Blood plasma

I⁻ (iodide in plasma)

Thyroid follicle

I₂ (Iodine)

Peroxidase

Thyroglobulin

I⁻ + H₂O₂

Thyroid uptake of iodide

NIS (Na+/I- Symporter)

TPO

I⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻سبوع


Colloid

Triiodothyronine (T₃)

Tetraiodothyronine (T₄)

Bound to thyroglobulin

Endocytosis stimulated by TSH

Plasma carrier protein

Thyroid hormone secretion

MIT (Monoiodothyrosine)

DIT (Diiodothyrosine)
Effects of thyroid hormones

- Fetal brain & skeletal maturation
- Increase in basal metabolic rate
- Inotropic & chronotropic effects on heart
- Increases sensitivity to catecholamines
- Stimulates gut motility
- Increase bone turnover
- Increase in serum glucose, decrease in serum cholesterol
- Conversion of carotene to vitamin A
- Play role in thermal regulation
Increase BMR ( Basal Metabolic Rate )

- ↑cellular metabolic activity by :
  - ↑ size, total membrane surface & number of mitochondria
  - ↑ ATP formation
  - ↑ active transport of ions ( Na⁺, K⁺ )

Promote growth & development of the brain during fetal life and for the first few years of postnatal life
Carbohydrate metabolism

- enhanced glycolysis, gluconeogenesis,
- GI absorption & insulin secretion

Fat metabolism

- enhanced fat metabolism
- Accelerates the oxidation of free fatty acids by the cells
- plasma cholesterol, phospholipids & triglycerides

Body weight

↑ the appetite, food intake, GI motility  but ↓ the body weight
• Cardiovascular system
  • vasodilatation
  • ↑ blood flow
  • ↑ cardiac output
  • ↑ heart rate

• Respiratory
  • ↑ the rate and depth respiration

• CNS
  • extreme nervous & psychoneurotic tendency

• Muscle
  • make the muscles react with vigor --->
  • muscle tremor (10-15 times/sec)

• Sleep: extreme fatigue but is difficult to sleep
Causes, Clinical Features & Consequences of Hypothyroidism

Congenital Hypothyroidism
Acquired Hypothyroidism
Etiology

• Congenital
• Acquired
  – Primary
  – Secondary
  – Tertiary
Congenital Hypothyroidism

- Occurs in about 1/4000 live birth
- Thyroxin is important for CNS development and postnatal growth
- The most frequent cause is congenital absence of the thyroid gland (athyrosis)
- Presentations may include cyanosis, prolonged hyperbilirubinemia, poor feeding, hoarse cry, umbilical hernia, respiratory distress, macroglossia, large fontanelle, and delayed skeletal maturation
- Rarely, neonatal hypothyroidism is transient
Congenital Hypothyroidism

Etiology

1) Thyroid dysgenesis
- Idiopathic:
  - Commonest cause in 95% of cases
    - Athyreosis (40%)
    - Hypoplasia (40%)
    - Ectopia (base of tongue, midline) (20%)

2) Thyroid dyshormonogenesis (A.R) (10%)

3) Hypothalamic-pituitary hypothyroidism
- Anencephaly, holoprosencephaly, S.O.D
- Idiopathic
Congenital Hypothyroidism

4) Transient hypothyroidism
   – Maternal TRAB
   – Maternal ingestion of goitrogen

5) Drugs

6) Iodine excess

7) Iodine deficiency
Anti-thyroid Drugs and fetus

- Thionamides
  - PTU & MZT
- Iodide
- Lithium
- Amiodarone
- Radioiodine
  - After 10-12 wk gestation can damage fetal thyroid gland
Presentations of congenital hypothyroidism

• Macroglosia
• Prolonged hyperbilirubinemia
• Poor feeding
• Hoarse cry
• Decreased activity
• Constipation
• Umbilical hernia
• Dry yellow skin
• Large fontanelle
• Delayed skeletal maturation
**Neonatal screening for congenital hypothyroidism**

- Routine in most countries worldwide
- Filter paper blood spot measuring TSH
  - Why ??
- Clinical manifestations at birth, usually are subtle or even absent (passive transplacental maternal thyroxin)
- At birth, surge of TSH (stress of delivery) up to 30-40 µu/ml
- Early detection will prevent mental retardation or decreasing IQ of affected neonates
- Thyroxin is important for CNS development from birth till 3 years of life
- Screening program will miss 2ry/ tertiary cases
- The program is hampered by a high rate of false positive results
Acquired Hypothyroidism

• More common than hyperthyroidism
• 99% is primary (< 1% due to TSH deficiency)
• Hashimoto’s
  – most common thyroid problem (4% of population)
  – most common cause in iodine-replete areas
  – chronic lymphocytic thyroiditis
  – Associated with TPO antibodies (90%), less commonly Tg antibodies
• Iatrogenic Hypothyroidism from radioactive iodine therapy
Acquired Hypothyroidism

- **Subacute thyroiditis**
  - Painful, often radiates to the ear
  - c/o malaise, pharyngitis, fatigue, fever, neck pain/swelling
  - Viral etiology (URI/ pharyngitis)
  - self-limited. Can tx inflammation w/ ASA, NSAID’s or steroids

- **Suppurative/ Acute Infectious thyroiditis**
  - Infections of the thyroid are rare
    - normally protected from infection by its thick capsule
  - Bacterial >> fungal, mycobacterial or parasitic
  - Pt’s are acutely ill w/ a painful thyroid gland
    - assoc w/ fever/chills, anterior neck pain/swelling, dysphagia and dysphonia
Acquired Hypothyroidism

• **Symptoms**
  – General Slowing Down
  – Lethargy/somnolence
  – Depression
  – Modest Weight Gain
  – Cold Intolerance
  – Hoarseness
  – Dry skin
  – Constipation (↓ peristaltic activity)
  – General Aches/Pains
    • Arthralgias or myalgias (worsened by cold temps)
  – Brittle Hair
  – Menstrual irregularities
    • Excessive bleeding
    • Failure of ovulation
  – ↓ Libido
Acquired Hypothyroidism

Examination

• Dry, pale, course skin with yellowish tinge
• Periorbital edema
• Puffy face and extremities
• Sinus Bradycardia
• Diastolic HTN
• ↓ Body temperature
• Delayed relaxation of reflexes
• Megacolon (↓ peristaltic activity)
• Pericardial/ pleural effusions
• Congestive heart failure
• Non-pitting edema
• Hoarse voice
• Myopathy
Goiter

• A swollen thyroid gland
• Assessment;
  – how big, how quickly has it developed, is it smooth or nodular, is it painful, any associated lymph nodes, any sudden changes, is it big enough to cause local symptoms (e.g. breathing problems)
Myxedema

Figure 20–8. Myxedema. (Reproduced, with permission, from Greenspan FS, Gardner DG [editors]: Basic and Clinical Endocrinology, 6th ed. McGraw-Hill, 2001.)
Hypothyroidism --- loss of scalp hair
Hypothyroidism with short stature
Diagnosis

Congenital hypothyroidism
- Thyroid hormone level
- TSH
- Thyroid scan

Acquired Hypothyroidism
- TSH
- fT4
- Thyroid antibodies
- Thyroid ultrasound
- **TSH**: low in secondary hypothyroidism
  - high in primary hypothyroidism
- **TRH test**: to differentiate between secondary & Tertiary hypothyroidism
Euthyroid sick syndrome

- Abnormalities in thyroid function tests observed with systemic non thyroidal illness
- Cytokine mediated
- Reduced TRH release, TSH response, T4 production/release, T4 to T3 conversion and TBG production
- Increased somatostatin secretion
- Inhibitory effects of dopamine and glucocorticoid on TRH action
- Very low T4 values have a poor prognosis
Treatment

• L-thyroxin replacement should be started as soon as possible
• If treatment is delayed > 2 months of life, > 75% risk of hypothyroidism
• On the other hand, delayed treatment of hyperthyroidism will lead to advanced skeletal maturation, craniosynostosis and intellectual deficits
• L-Thyroxin is the main drug for treatment of hypothyroidism, whatever is the cause
## Treatment

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Causes, Clinical Features & Consequences of Hyperthyroidism
Hyperthyroidism (Thyrotoxicosis)

Definition

• Excessive secretion of T3 & T4
• Affects metabolic processes in all body organs
• Hyperthyroidism is 4-10 times more prevalent in women
• Most common endocrine disease second only to diabetes as the most occurring endocrine disease
Thyrotoxicosis

Causes

Transient

1. Neonatal thyrotoxicosis
2. Infectious: Acute & subacute thyroiditis
3. Drug – induced: Amiodarone, interferon & interleukin
4. Iatrogenic
Thyrotoxicosis

Causes

Persistent

1. Graves’ disease
2. Toxic multinodular goiter
3. Toxic solitary adenoma
4. Central (pituitary origin)
Neonatal Thyrotoxicosis

- Only occur with 5% of thyrotoxic mothers
- Severity consistent in future pregnancies
- 20% mortality if untreated
- Evolves rapidly, evident by day 7 of life, unless TRAB blocking antibody is present
- Associate with cranial synostosis and learning difficulties, if not treated
- Fetal thyrotoxicosis in rats leads to abnormal CNS myelination
- Parents should be aware of potential learning problems (early school years should be monitored)
Neonatal hyperthyroidism born to mother with Graves’ disease
Grave’s disease

Pathogenesis

• T-cell dependent autoimmune disease
• 60% have HLA association with A1, B8, DR3, DR4, DR5
• Autoimmune disorder that results in production of antibodies directed against thyroid antigens:
  – TSH receptors
  – Thyroglobulin
  – Thyroid peroxidase
Subacute Thyroiditis

• Clinical course lasts weeks to months
• Acute phase (2-6/52) with clinical and biochemical hyperthyroidism
• Recovery phase (weeks-months) transient hypothyroidism then euthyroidism
• Clinically, history of sore throat, fever, tender goiter, cervical lymphadenopathy
• High ESR, negative antibodies and absent radioactive I\textsuperscript{131} uptake
Hyperthyroidism

- May result in significant morbidity, mortality & even death
- **Symptoms**
  - Jittery, shaky, nervous
  - Difficulty concentrating
  - Emotional lability
  - Insomnia
  - Rapid HR, palpitations, Feeling Hot
  - Weight Loss
  - Diarrhea
  - Fatigue
  - Menses : lighter flow, shorter duration
Hyperthyroidism

• Exam
  – Eye findings (20%)
  – Goiter
  – Thyroid bruit or thrill
  – Tachycardia: Sinus Tachycardia, Atrial Fibrillation
  – Flow murmur
  – Systolic hypertension
  – Hyperreflexia
  – Tremors
  – Proximal muscle weakness
  – Clubbing
  – Onycholysis (<1%)
    • separation of nail from the nailbed
  – Dermopathy (1%)
Thyrotoxicosis

- Heart: Increased heart rate, contractility and cardiac output
- Skeletal muscles: Proximal myopathy, easy fatigability and muscle atrophy
- Gonads: Irregular menstrual cycles, impotence
- Liver: Low cholesterol LDL & apolipoprotein
- Bone: Increased bone turnover, osteoporosis & increased risk of fracture
Grave's ophthalmopathy

- The pathogenesis of infiltrative ophthalmopathy is poorly understood
- It may occur before the onset of hyperthyroidism or as late as 15 to 20 years
- The clinical course of ophthalmopathy is independent of the clinical course of hyperthyroidism
- Infiltrative ophthalmopathy may result from immunoglobulins directed to specific antigens in the extraocular muscles & orbital fibroblasts
- The antibodies are distinct from those initiating Graves'-type hyperthyroidism
Clinical Characteristics of Exophthalmos

- Proptosis
- Corneal Damage
- Periorbital edema
- Chemosis
- Conjunctival injection
- Extraocular muscle impairment
- Optic neuropathy

Graves' Disease

- Goiter
- Hyperthyroidism
- Exophthalmos
- Localized myxedema
- Thyroid acropachy
- Thyroid stimulating immunoglobulins

Clinical Characteristics of Goiter in Graves’ Disease

- Diffuse increase in thyroid gland size
- Soft to slightly firm
- Non-nodular
- Bruit and/or thrill
- Mobile
- Non-tender
- Without prominent adenopathy

Lid Lag in Thyrotoxicosis

Normal | Lid Lag
Hyperthyroid Eye Disease

- Hyperthyroidism (any cause)
  - Lid lag, lid retraction and stare
  - Due to increased adrenergic tone stimulating the levator palpebral muscles.

- True Graves’ Ophthalmopathy
  - Proptosis
  - Diplopia
  - Inflammatory changes
    - Conjunctival injection
    - Periorbital edema
    - Chemosis
  - Due to thyroid autoAb’s that cross-react w/ Ag’s in fibroblasts, adipocytes, + myocytes behind the eyes.
“Exophthalmos”
Grave’s ophthalmopathy
Hyperthyroid Eye Disease
Graves’ Dermopathy

Thyroid Dermopathy
– Thickening and redness of the dermis
  • Due to lymphocytic infiltration
Thyroid Acropachy

Thyroid acropachy. This is most marked in the index fingers and thumbs.
Tremor of the hand
Onycholysis of Thyrotoxicosis

Distal separation of the nail plate from nail bed (Plummer’s nails)

Thyroid Acropachy

- Clubbing of fingers
- Painless
- Periosteal bone formation and periosteal proliferation
- Soft tissue swelling that is pigmented and hyperkeratotic

Periosteal Proliferation

Clubbing of fingers
Diagnosis

• TSH level usually < 0.05 μu / ml
• 95% of cases, high FT4 & FT3
• In 5% high FT3 with normal T4 (T3 Thyrotoxicosis)
• Thyroid receptor (TRAB) are usually elevated at diagnosis
• Antibodies against thyroglobulin, peroxidase or both are present in the majority of patients
Thyroid Scan in Thyrotoxicosis

Graves’ Disease
Multinodular Goiter

Follicular Adenoma
Subacute Thyroiditis
Thyrotoxicosis - Treatment

- Three modalities for more than last 50 years
- Radioactive iodine, antithyroid drugs & surgery
- None is optimal
- None interrupts the autoimmune process
- Each has a drawbacks
- There is no treatment for underlying cause
- No other research options so far
Neonatal Thyrotoxicosis

Treatment
1) Lugol’s iodine
   • 1 drop tid for 1-2 / 7
   • Dramatic coarse therapy
   • Blocks T4 release, synthesis and I uptake
     (Wolf Chaikoff effect)
2) Propranolol
3) Carbimazole
   will take several days to have an effect on T4 synthesis
Hyperthyroidism (Treatment)

1) β-blockers (symptom control)
   – Propranolol (Inderal ®)
   – Atenolol (Tenormin ®)
   – Metoprolol (Lopressor ®)

2) 131-RAIA (70% thyroidologists prefer)
   – Dosing
     • Graves: 10-15 mCi
     • Toxic MNG/Adenoma: 20-30 mCi
   – Absolute contraindications
     • Pregnancy and lactation (excreted in breast milk)!
   – Pregnancy should be deferred for at least 6 months following therapy with radio-active 131
   – It is advisable to avoid 131-Rdio-active iodine therapy in patients with active moderate→ severe Graves’ ophthalmopathy.
Hyperthyroidism (Treatment)

3) **Antithyroid Drugs** (30% thyroidologists prefer)
   - Propylthiouracil (PTU)
     • 100 mg bid-tid to start
   - Methimazole
     • 10X more potent the PTU
     • 10 mg bid-tid to start
   - Complications of ATD’s
     • Agranulocytosis (1/200-500)
       – usually presents w/ acute pharyngitis/ tonsilitis or pneumonia.
     • Rash
     • Hepatic necrosis, Cholestatic jaundice
     • Arthralgia
4) **Surgery** (sub-total thyroidectomy)

- **Indications**
  - Patient preference
  - Large or symptomatic goiters
  - When there is question of malignancy
- **Need to be euthyroid prior to surgery**
  - To ↓ the risk of arrhythmias during induction of anesthesia
  - To ↓ the risk of thyroid storm post operatively
  - ATD’s + β-blockers
- **Risks**
  - Permanent hypoparathyroidism
  - Recurrent laryngeal nerve problems
  - Permanent hypothyroidism
موظفين باذن
الله تعالى