

# Nonneoplastic Diseases of the Thyroid

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# Introduction

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- Basic Science
- Diagnostic Issues
- Hypothyroidism
- Thyrotoxicosis
- Thyroiditis
- Interactive Case Presentation
- Controversies/New Areas of Interest

# Introduction

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- Nonneoplastic diseases of the thyroid affect nearly 3/4 of a billion worldwide
  - iodine deficiency common worldwide
  - iodine excess common in US
    - ?contribution to autoimmune diseases
- Thyroid surgery is the most common neck surgery performed by the Otolaryngologist

# Basic Science - Anatomy

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- The thyroid is located on the anterior superior portion of the trachea near the third tracheal ring
- Arterial supply is from superior and inferior thyroid arteries
- Venous drainage from three paired thyroid veins: superior, middle, inferior
- RLN runs with inferior thyroid artery, SLN with the superior thyroid artery

# Basic Science - Histology

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- Functional unit of thyroid gland is the thyroid follicle
  - cuboidal epithelial cells surrounding colloid filled lumen
  - active follicles are smaller
  - responsible for thyroid hormone synthesis
- Parafollicular “C” Cells (“Clear” cells)
  - secrete calcitonin
  - respond to serum ionized calcium levels

# Basic Science - Embryology

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- Thyroid gland is derived from invagination of endoderm of first branchial pouch near lingual bud
- Grows inferiorly around the hyoid to anterior trachea
  - remnant is thyroglossal duct
  - foramen cecum is remnant
- Aberrant thyroid tissue can be located anywhere along thyroglossal duct

# Basic Science - Embryology

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- Parafollicular Cells are of different origin than thyroid follicular cells
  - these cells originate from ultimobranchial apparatus near inferior portion of pharyngeal pouch
  - ultimobranchial organ seen in lower vertebrates as a separate organ

# Basic Science - Physiology

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- Primary function of the thyroid gland is the secretion of thyroid hormones
  - T4 is primary released hormone
  - T3 at least 10 times more active
  - T4 is converted to T3 peripherally
- Production of thyroid hormones is regulated in normal gland by thyroid stimulating hormone (TSH) from the anterior pituitary gland

# Basic Science - Physiology

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- T4 and T3 act as negative feedback to the release of TSH
  - TSH response is “logarithmic”
- TSH is stimulated by thyroid releasing hormone (TRH) of the hypothalamus
  - TRH is believed to be continually secreted
  - Pituitary gland is more sensitive to negative feedback of T4 and T3 than TRH

# Basic Science - Physiology

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- Thyroid Hormone Secretion:
  - TSH joins follicular cell receptor, then:
  - cAMP mediates:
    - active transport of iodide
    - synthesis of thyroglobulin (TG) by ER
  - Thyroperoxidase (TPO) mediates:
    - conversion of iodide to iodine
    - coupling of iodine to tyrosine and TG (colloid)
  - Lysosomes release T4/T3

# Diagnostic Issues

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- No accurate test measures peripheral thyroid hormone action
- TSH, serum T4, free T4 index, T3 and RAIU are most commonly used tests
  - TSH: most useful test. Sensitive to T4/T3
  - Measures total T4. Most protein bound!
  - FT4I: *mathematically estimates* FT4
  - RAIU: I123 scan. Measures activity of gland

# Diagnostic Issues - Antibodies

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- Antimicrosomal and antithyroglobulin antibodies are seen in 90% of pts with Hashimoto's Thyroiditis
  - also seen with increasing age and nonthyroid diseases
- TSH Receptor Antibodies are seen with Graves' Disease
  - may be stimulatory or competitive inhibitors

# Hypothyroidism

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## ■ Physical Exam

### – Mild/Moderate Disease

- Lethargy, hoarseness, hearing loss, thick and dry skin, constipation, cold intolerance, stiff gait

### – Sever Disease (Myxedema Coma)

- coma, refractory hypothermia, bradycardia, pleural effusions, electrolyte imbalances, hypoventilation, seizures

- Tx: IV steroids, T4, ventilatory support, thermal support, antiseizure medications

# Hypothyroidism

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- Primary: abnormalities of the gland
- Secondary: abnormalities of the pituitary gland
- Tertiary: abnormalities of the hypothalamus (rare)
- Peripheral: end organ resistance
  - *c-erb A* gene of chromosomes 17 and 3 code for cellular hormone receptors

# Hypothyroidism - Primary

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- Autoimmune Diseases are the most common cause of hypothyroidism
  - Hashimoto's Thyroiditis
  - Graves' disease (usually *hyper*thyroidism)
  - Iodide excess (spina bifida, renal failure)
- Iatrogenic causes are the next most common causes
  - Surgery, radioiodine ablation, inadequate replacement, Li, Amiodarone, iodide

# Hypothyroidism - Congenital

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## ■ Cretinism

- severe hypothyroidism in the newborn
- PE: protuberant abdomen, face, flat nose, yellow skin, constipation, lethargy, feeding difficulties, hoarse, MR
- Endemic: goiter present. Maternal IgG or maternal antithyroid medications
- Sporadic: thyroid agenesis (Di George syndrome most common)

# Juvenile Hypothyroidism

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- Usually due to hormonal synthesis defect such as TPO or to *c-erb A* mutation
- PE: goiter, delayed maturation, testicular enlargement/precocious menarche
- NOT usually MR- recovery is general rule with thyroxine

# Thyrotoxicosis

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- Defn: state where exposed tissue responds to an excess of T4/T3
- PE: nervousness, tremors, sweating, heat intolerance, palpitations, afib, wt loss, amenorrhea, weakness
- Etiologies:
  - Graves' disease most common
    - toxic multi and uninodular goiters, carcinoma and pituitary abnormalities

# Thyrotoxicosis - Graves' Dz

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## ■ Graves' Disease

- Autoimmune: IgG antibodies against TSH receptors. May be stimulatory (most common) or inhibitory
  - often similar to Hashimoto's Thyroiditis, particularly when hypothyroidism present
- Soft goiter usually present
- Histology: "too many follicular cells, too little colloid"

# Graves' Disease - Continued

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## ■ Treatment

- antithyroid medications, RAI, surgery
- Antithyroid medications
  - Iodide: transient. Inhibits organification, proteolysis, angiogenesis
    - thyrotoxicosis in euthyroid Graves' disease!
  - Thionamides: propylthiouracil, methimazole
    - TPO inhibitor, peripheral T4 conversion to T3
    - Require 4-8 to work
  - Beta blockers: block peripheral conversion, ameliorates adrenergic side effects.

# Graves' Disease, Continued

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## ■ Radioiodine ablation

- Most commonly used procedure in US
- Indicated when medical therapy fails or in patients unable/unwilling to take meds
- PTU/Iodide usually used pre-ablation as less dose is required
- Must stop PTU/Iodide 3 days prior to avoid thyroid storm

# Graves' Disease, Continued

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## ■ Total/Subtotal Thyroidectomy

- Less commonly used than RAI, but many feel it is the procedure of choice
- Always procedure of choice in pregnant women requiring surgery
- PTU/beta blockers required preoperatively to avoid thyroid storm

# Toxic Adenoma

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- Caused by a “Hot Nodule”
  - thyroxicosis may be caused by hot nodule, but not all hot nodules cause thyrotoxicosis
    - those larger than 3 cm usually required
  - Dx: low/absent TSH, high T4, RAIU: hot nodule
  - Tx: RAI ablation versus surgery

# Toxic Multinodular Goiter

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- Common in areas of iodide deficiency
- Dx: multinodular gland, sx of hyperthyroidism, low/absent TSH, high T4. RAIU: multiple hot nodules
- Tx: RAI ablation versus surgery. Exogenous T4 causes thyrotoxicity
- Histology: difficult to distinguish from adenoma

# Thyrotoxicosis - Rare Causes

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- Thyrotropin Induced Thyrotoxicosis is a pituitary adenoma until proven otherwise. Hyperplasia/Ca are rare.
  - high TSH, high T4, requires MRI
- Trophoblastic tumors
  - hydatidiform moles and germ cell tumors secrete thyrotropic beta HCG.
  - Tx: surgical removal

# Thyroid Storm

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- Exceedingly high levels of thyroid hormone
- Usually preceded by stress: infection, surgery, RAI ablation
- PE: heart failure/afib, coma, hyperthermia
- Tx: IV steroids, PTU, propranolol, ice baths

# Thyroiditis

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- Defn: thyroid disorders marked by infiltration of leukocytes, fibrosis or both
- Types:
  - Acute suppurative
  - Painful (de Quervain's)
  - Postpartum
  - Hashimoto's
  - Fibrous (Reidel's)

# Thyroiditis - Continued

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- Acute Suppurative Thyroiditis
  - Bacterial infection, usually *S. aureus* or *S. pneumo*. Usually preceded by trauma
  - Tx: IV abx, I and D if abscess
- Painful Thyroiditis (de Quervain's)
  - Unknown virus
  - Painful thyroid following URI
  - Hyperthyroidism followed by hypothyroidism - lasts 2 month
  - Tx: beta blockers/thyroxine supportive

# Thyroiditis, Continued

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## ■ Postpartum Thyroiditis

- “Silent” thyroiditis of pregnancy and first few postpartum months
- Associated with Graves’ disease and other autoimmune diseases
- Tx: beta blockers/synthroid as needed
- Usually self limiting, but high titers of antibodies heralds long term disease

# Thyroiditis, Continued

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- Hashimoto's Thyroiditis
  - Most common thyroiditis
  - Antimicrosomal and antithyroglobulin antibodies, but anti TSH receptor Abs seen
  - Associated with other autoimmune diseases
  - Pts usually euthyroid
  - 60-80 time increase in lymphoma

# Hashimoto's Disease, Cont.

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- Histology: "Askanazy changes" - predominant lymphocytes with germinal centers. Scant follicles
- Tx:
  - Hypothyroid patients: synthroid
  - Hyperthyroid: antithyroid medications
  - Surgery reserved for failure of suppression or suspicion of lymphoma

# Case

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- A 32 yohf presents from Harlingen because "the doctor says my thyroid is bad." She presents with her husband and her three children, the youngest a "FLK" newborn. Her MD is unavailable.

# Case, Continued

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- PMH: anxiety
- PSH: none
- SocHx: no tob, etoh. Home schools eldest child because "he's lazy and won't pay attention to the teacher or do any work."
- All: NKDA
- MEDS: Xanax prn

# Case, Continued

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- PE: 133/77, 20, 38.1, 140
  - Thin, anxious woman
  - HEENT: ?slight exophthalmos. Neck: mild/mod goiter, several “nodules” palpated
  - Neuro: 2-12 intact, slightly tremulous
  - Pulm: CTA
  - CV: irregular, tachycardic

# Case, continued

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## ■ Labs/Studies

- TSH: 0.2 (2-10)
- FT4I: 34 (2-10)
- RAI Scan: uptake in all areas, two small hyperfunctioning nodes on left, one hypofunctioning nodule on right
- Thyroid antibodies: positive for anti TSH antibodies, antimicrosomal antibodies and antithyroglobulin antibodies

# Controversies

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- Treatment of Hyperthyroidism
  - Antithyroid medications versus RAI ablation versus surgery
- Indications for Surgery in goiter
  - compressive/obstructive symptoms
  - failure to suppress
  - Multinodular goiter

# New Areas of Interest

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- Neurodevelopment and Peripheral Resistance to Thyroid Hormones
  - Most common cause known to be malfunctioning peripheral TSH receptors
  - *c-erb A* gene isolated
  - Attempts being made to “splice” *c-erb A* into cells
    - review of this topic: Haures, P. Resistance to Thyroid Hormones: Implications for Neural Developments, *Toxicology and Health*, 1998.