Benign Thyroid Diseases

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Grand Rounds Presentation
May 2006
History

- **Goiter**
  - Fist described in China in 2700 BC

- **Thyroid Function**
  - Da Vinci – thyroid is designed to fill empty spaces in the neck
  - Parry – thyroid works as a buffer to protect the brain from surges in blood flow
  - Roman physicians – thyroid enlargement is a sign of puberty

- **Cures**
  - “application of toad’s blood to the neck”
  - “stroking of the thyroid gland with a cadaverous hand”
Surgical advances

- **500 AD**
  - Abdul Kasan Kelebis Abis performed the first goiter excision in Baghdad.
  - Procedure: unknown

- **1200’s AD**
  - Advancements in goiter procedures included applying hot irons through the skin and slowly withdrawing them at right angles. The remaining mass or pedicled tissue was excised.
  - Patients were tied to the table and held down to prevent unwanted movement.
  - Most died from hemorrhage or sepsis.

- **1646 AD**
  - Wilhelm Fabricus performed a thyroidectomy with standard surgical scalpels.
  - The 10 y/o girl died, and he was imprisoned

- **1808 AD**
  - Guillaume Dupuytren performed a total thyroidectomy.
  - The patient died postoperatively of “shock”
Surgical advances

1866

“...If a surgeon should be so foolhardy as to undertake it [thyroidectomy] ... every step of the way will be environed with difficulty, every stroke of his knife will be followed by a torrent of blood, and lucky will it be for him if his victim lives long enough to enable him to finish his horrid butchery.”

– Samuel David Gross
Surgical advances

1883

Kocher’s performs a retrospective review

- 5000 career thyroidectomies
- Mortality rates decreased
  - 40% in 1850 (pre-Kocher & Bilroth)
  - 12.6% in 1870’s (Kocher begins practice)
  - 0.2% in 1898 (end of Kocher’s career)
- Many patients developed cretinism or myxedema

His conclusions ....
Surgical advances

In presentation to the German Surgical Congress ...

“...the thyroid gland in fact had a function....”

- Theodor Kocher, 1883
Medical Advances

- **1820 AD**
  - Johann Straub and Francois Coindet found that use of seaweed (iodine) reduced goiter size and vascularity.

- **1830 AD**
  - Graves and von Basedow describe a toxic goiter condition they referred to as “Merseburg Triad” – goiter, exophthalmos, palpitations.
Thyroid Physiology
Iodine transport

- Na\(^{+}\)/I\(^{-}\) symport protein controls serum I\(^{-}\) uptake
- Based on Na\(^{+}\)/K\(^{+}\) antiport potential
- Stimulated by TSH
- Inhibited by Perchlorate
Thyroid hormone formation

- **Thyroid Peroxidase (TPO)**
  - Apical membrane protein
  - Catalyzes Iodine organification to tyrosine residues of thyroglobulin
  - Antagonized by methimazole, PTU

- **Iodine coupled to Thyroglobulin**
  - Monoiodotyrosine (Tg + one I⁻)
  - Diiodotyrosine (Tg + two I⁻)

- Pre-hormones secreted into follicular space
Wolff-Chaikoff Effect

- Increasing doses of $I^-$ increase hormone synthesis initially.
- Higher doses cause cessation of hormone formation.
- This effect is countered by the Iodide leak from normal thyroid tissue.
- Patients with autoimmune thyroiditis may fail to adapt and become hypothyroid.
Jod-Basedow Effect

- Opposite of the Wolff-Chaikoff effect
- Excessive iodine loads induce hyperthyroidism
- Observed in hyperthyroid disease processes
  - Graves’ disease
  - Toxic multinodular goiter
  - Toxic adenoma
- This effect may lead to symptomatic thyrotoxicosis in patients who receive large iodine doses from
  - Dietary changes
  - Contrast administration
  - Iodine containing medication (Amiodarone)
Thyroid Hormone Control
TRH

- Produced by Hypothalamus
- Release is pulsatile, circadian
- Downregulated by T₃
- Travels through portal venous system to adenohypophysis
- Stimulates TSH formation
TSH

- Produced by Adenohypophysis Thyrotrophs
- Upregulated by TRH
- Downregulated by $T_4$, $T_3$
- Travels through portal venous system to cavernous sinus, body.
- Stimulates several processes
  - Iodine uptake
  - Colloid endocytosis
  - Growth of thyroid gland
TSH Response

Graph showing the TSH response to TRH with different doses of T3 and T4.
Thyroid Hormone

- Majority of circulating hormone is $T_4$
  - 98.5% $T_4$
  - 1.5% $T_3$

- Total Hormone load is influenced by serum binding proteins
  - Albumin 15%
  - Thyroid Binding Globulin 70%
  - Transthyretin 10%

- Regulation is based on the free component of thyroid hormone
Hormone Binding Factors

- **Increased TBG**
  - High estrogen states (pregnancy, OCP, HRT, Tamoxifen)
  - Liver disease (early)

- **Decreased TBG**
  - Androgens or anabolic steroids
  - Liver disease (late)

- **Binding Site Competition**
  - NSAID’s
  - Furosemide IV
  - Anticonvulsants (Phenytoin, Carbamazepine)
Thyroid Evaluation

- TRH
- TSH
- Total $T_3$, $T_4$
- Free $T_3$, $T_4$
- RAIU
- Thyroglobulin
- Antibodies: Anti-TPO, Anti-TSHr
Thyroid Evaluation

Figure 118-2. Algorithm for using the TSH level in the evaluation of thyroid function.
RAIU

- Scintillation counter measures radioactivity after $I^{123}$ administration.

- Uptake varies greatly by iodine status
  - Indigenous diet (normal uptake 10% vs. 90%)
  - Amiodarone, Contrast study, Topical betadine

- Elevated RAIU with hyperthyroid symptoms
  - Graves’
  - Toxic goiter

- Low RAIU with hyperthyroid symptoms
  - Thyroiditis (Subacute, Active Hashimoto’s)
  - Hormone ingestion (Thyrotoxicosis factitia, Hamburger Thyrotoxicosis)
  - Excess $I^-$ intake in Graves’ (Jod-Basedow effect)
  - Ectopic thyroid carcinoma (Struma ovarii)
Iodine states

- Normal Thyroid
- Inactive Thyroid
- Hyperactive Thyroid
Common Thyroid Disorders
Goiter

- **Goiter**: Chronic enlargement of the thyroid gland not due to neoplasms
- **Endemic goiter**
  - Areas where > 5% of children 6-12 years of age have goiter
  - Common in China and central Africa
- **Sporadic goiter**
  - Areas where < 5% of children 6-12 years of age have goiter
  - *Multinodular goiter* in sporadic areas often denotes the presence of multiple nodules rather than gross gland enlargement
- **Familial**
Goiter

- **Etiology**
  - **Hashimoto’s thyroiditis**
    - Early stages only, late stages show atrophic changes
    - May present with hypo, hyper, or euthyroid states
  - **Graves’ disease**
    - Due to chronic stimulation of TSH receptor
  - **Diet**
    - Brassica (cabbage, turnips, cauliflower, broccoli)
    - Cassava
  - **Chronic Iodine excess**
    - Iodine excess leads to increased colloid formation and can prevent hormone release
    - If a patient does not develop iodine leak, excess iodine can lead to goiter
  - **Medications**
    - Lithium prevents release of hormone, causes goiter in 6% of chronic users
  - **Neoplasm**
Goiter

Pathogenesis

- Iodine deficient areas
  - Heterogeneous response to TSH
  - Chronic stimulation leads to multiple nodules
- Iodine replete areas
  - Thyroid follicles are heterogeneous in their growth and activity potential
  - Autopsy series show MNG >30%.

Thyroid function evaluation

- TSH, T4, T3
  - Overt hyperthyroidism (TSH low, T3/T4 high)
  - Subclinical hyperthyroidism (TSH low, T3/T4 normal)

Determination of thyroid state is key in determining treatment
Non-Toxic Goiter

- Cancer screening in non-toxic MNG
  - Longstanding MNG has a risk of malignancy identical to solitary nodules (<5%)
  - MNG with nodules < 1.5 cm may be followed clinically
  - MNG with non-functioning nodules > 4cm should be excised
    - No FNA needed due to poor sensitivity
    - Incidence of cancer (up to 40%)
- FNA in MNG
  - Sensitivity 85% - 95%
  - Specificity 95%
  - Negative FNA can be followed with annual US
  - Insufficient FNA’s should be repeated
  - Incocclusive FNA or papillary cytology warrants excision
- Hyperfunctioning nodules may mimic follicular neoplasm on FNA
Non-Toxic Goiter

- **Treatment options** (no compressive symptoms)
  - US follow-up to monitor for progression
  - Thyroid suppression therapy
    - May be used for progressive growth
    - May reduce gland volume up to 50%
    - Goiter regrowth occurs rapidly following therapy cessation
  - Surgery
    - Suspicious neck lymphadenopathy
    - History of radiation to the cervical region
    - Rapid enlargement of nodules
    - Papillary histology
    - Microfollicular histology (?)
Non-Toxic Goiter

Treatment options (compressive symptoms)

- RAI ablation
  - Volume reduction 33% - 66% in 80% of patients
  - Improvement of dysphagia or dyspnea in 70% - 90%
  - Post RAI hypothyroidism 60% in 8 years
  - Post RAI Graves’ disease 10%
  - Post RAI lifetime cancer risk 1.6%

- Surgery
  - Most commonly recommended treatment for healthy individuals
Toxic Goiter

- Evaluate for
  - Graves’ disease
    - Clinical findings (Pretibial myxedema, Ophthalmopathy)
    - Anti-TSH receptor Ab
    - High RAUI
  - Thyroiditis
    - Clinical findings (painful thyroid in Subacute thyroiditis)
    - Low RAUI
  - Recent Iodine administration
    - Amiodarone
    - IV contrast
    - Change in diet

- FNA evaluation
  - Not indicated in hyperthyroid nodules due to low incidence of malignancy
  - FNA of hyperthyroid nodules can mimic follicular neoplasms
Toxic Goiter

- Risks of hyperthyroidism
  - Atrial fibrillation
  - Congestive Heart Failure
  - Loss of bone mineral density
  - Risks exist for both clinical or subclinical disease

- Toxic Goiter
  - Toxicity is usually longstanding
  - Acute toxicity may occur in hyperthyroid states (Jod Basedow effect) with
    - Relocation to iodine replete area
    - Contrast administration
    - Amiodarone (37% iodine)
Toxic Goiter

Treatment for Toxic MNG

- Thionamide medications
  - **Not indicated for long-term use due to complications**
  - May be used for symptomatic individuals until definitive treatment.

- Radioiodine
  - **Primary treatment for toxic MNG**
  - Large I$^{131}$ dose required due to gland size
  - Goiter size reduction by 40% within 1 year
  - **Risk of hypothyroidism** 11% - 24%
  - May require second dose

- Surgery
  - **Used for compressive symptoms**
  - **Hypothyroidism occurs in up to 70% of subtotal thyroidectomy patients**
  - Pre-surgical stabilization with thionamide medications
  - Avoid SSKI due to risk for acute toxic symptoms
Graves’ Disease

- Most common cause of thyrotoxicosis in the industrialized world
- Autoimmune condition with anti-TSHr antibodies
- Onset of disease may be related to severe stress which alters the immune response
- Diagnosis
  - TSH, T₄, T₃ to establish toxicosis
  - RAIU scan to differentiate toxic conditions
  - Anti-TPO, Anti-TSAb, fT₃ if indicated

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Graves’ Disease

Treatment

- Beta blockers for symptoms

- Thionamide medications
  - May re-establish euthyroidism in 6-8 weeks
  - 40% - 60% incidence of disease remission
  - 20% incidence of allergy (rash, itching)
  - 0.5% incidence of potentially fatal agranulocytosis

- Radioiodine ablation
  - 10% incidence of hypothyroidism at 1 year
  - 55% - 75% incidence of hypothyroidism at 10 years
  - Avoid RAI in children and pregnancy

- Surgery
  - Large goiters not amenable to RAI
  - Compressive symptoms
  - Children, pregnancy
  - 50% - 60% incidence of hypothyroidism
Toxic Adenoma

- **Thyrotoxicosis**
  - Hyperfunctioning nodules <2 cm rarely lead to thyrotoxicosis
  - Most nodules leading to thyrotoxicosis are >3 cm.

- **Treatment Indications**
  - Post-menopausal female
    - Due to increased risk of bone loss
  - Patients over 60
    - Due to high risk of atrial fibrillation
  - Adenomas greater than 3 cm (?)
Toxic Adenoma

**Treatments**

- **Antithyroid medications**
  - Not used due to complications of long-term treatment

- **Radioiodine**
  - Cure rate > 80% (20 mCi I131)
  - Hypothyroidism risk 5% - 10%
  - Second dose of I131 needed in 10% - 20%
  - Patients who are symptomatically toxic may require control with thionamide medications before RAI to reduce risk of worsening toxicity.

- **Surgery**
  - Preferred for children and adolescents
  - Preferred for very large nodules when high I131 doses needed
  - Low risk of hypothyroidism

- **Ethanol Injection**
  - Rarely done in the US
  - May achieve cure in 80%
Hypothyroidism

- Symptoms – fatigability, coldness, weight gain, constipation, low voice
- Signs – Cool skin, dry skin, swelling of face/hands/legs, slow reflexes, myxedema
- Newborn – Retardation, short stature, swelling of face/hands, possible deafness
- Types of Hypothyroidism
  - Primary – Thyroid gland failure
  - Secondary – Pituitary failure
  - Tertiary – Hypothalamic failure
  - Peripheral resistance
Hypothyroidism

- Cause is determined by geography
  - Hashimoto’s in industrialized countries
  - May be due to iodine excess in some coastal areas

- Diagnosis
  - Low FT₄, High TSH (Primary, check for antibodies)
  - Low FT₄, Low TSH (Secondary or Tertiary, TRH stimulation test, MRI)

- Treatment
  - Levothyroxine (T₄) due to longer half life
  - Treatment prevents bone loss, cardiomyopathy, myxedema
Hypothyroidism

- Agenesis
- Thyroid destruction
  - Hashimoto’s thyroiditis
  - Surgery
  - $I_{131}$ ablation
  - Infiltrative diseases
  - Post-laryngectomy
- Inhibition of function
  - Iodine deficiency
  - Iodine administration
  - Anti-thyroid medications (PTU, Methimazole, Lithium, Interferon)
  - Inherited defects
- Transient
  - Postpartum
  - Thyroiditis
Hashimoto’s (Chronic, Lymphocytic)

- Most common cause of hypothyroidism
- Result of antibodies to TPO, TBG
- Commonly presents in females 30-50 yrs.
- Usually non-tender and asymptomatic
- Lab values
  - High TSH
  - Low T<sub>4</sub>
  - Anti-TPO Ab
  - Anti-TBG Ab
- Treat with Levothyroxine
Thyroiditis
Hashimoto's Thyroiditis

- Most common cause of goiter and hypothyroidism in the U.S.
- Physical
  - Painless diffuse goiter
- Lab studies
  - Hypothyroidism
  - Anti TPO antibodies (90%)
  - Anti Thyroglobulin antibodies (20-50%)
  - Acute Hyperthyroidism (5%)
- Treatment
  - Levothyroxine if hypothyroid
  - Triiodothyronine (for myxedema coma)
  - Thyroid suppression (levothyroxine) to decrease goiter size
    - Contraindications
      - Stop therapy if no resolution noted
    - Surgery for compression or pain.
Silent Thyroiditis
Post-partum Thyroiditis

- Silent thyroiditis is termed post-partum thyroiditis if it occurs within one year of delivery.

- Clinical
  - Hyperthyroid symptoms at presentation
  - Progression to euthyroidism followed by hypothyroidism for up to 1 year.
  - Hypothyroidism generally resolves

- Diagnosis
  - May be confused with post-partum Graves’ relapse

- Treatment
  - Beta blockers during toxic phase
  - No anti-thyroid medication indicated
  - Iopanoic acid (Telopaque) for severe hyperthyroidism
  - Thyroid hormone during hypothyroid phase. Must withdraw in 6 months to check for resolution.
Subacute Thyroiditis
DeQuervain’s, Granulomatous

- Most common cause of painful thyroiditis
- Often follows a URI
- FNA may reveal multinucleated giant cells or granulomatous change.
- Course
  - Pain and thyrotoxicosis (3-6 weeks)
  - Asymptomatic euthyroidism
  - Hypothyroid period (weeks to months)
  - Recovery (complete in 95% after 4-6 months)
Subacute Thyroiditis
DeQuervain’s, Granulomatous

- **Diagnosis**
  - Elevated ESR
  - Anemia (normochromic, normocytic)
  - Low TSH, Elevated T4 > T3, Low anti-TPO/Tgb
  - Low RAI uptake (same as silent thyroiditis)

- **Treatment**
  - NSAID’s and salicylates.
  - Oral steroids in severe cases
  - Beta blockers for symptoms of hyperthyroidism, Iopanoic acid for severe symptoms
  - PTU not indicated since excess hormone results from leak instead of hyperfunction
  - Symptoms can recur requiring repeat treatment
  - Graves’ disease may occasionally develop as a late sequellae
Acute Thyroiditis

- **Causes**
  - 68% Bacterial (S. aureus, S. pyogenes)
  - 15% Fungal
  - 9% Mycobacterial

- **May occur secondary to**
  - Pyriform sinus fistulae
  - Pharyngeal space infections
  - Persistent Thyroglossal remnants
  - Thyroid surgery wound infections (rare)

- **More common in HIV**
Acute Thyroiditis

**Diagnosis**
- Warm, tender, enlarged thyroid
- FNA to drain abscess, obtain culture
- RAIU normal (versus decreased in DeQuervain’s)
- CT or US if infected TGDC suspected

**Treatment**
- High mortality without prompt treatment
- IV Antibiotics
  - Nafcillin / Gentamycin or Rocephin for empiric therapy
- Search for pyriform fistulae (BA swallow, endoscopy)
- Recovery is usually complete
Riedel’s Thyroiditis

- Rare disease involving fibrosis of the thyroid gland

Diagnosis
- Thyroid antibodies are present in 2/3
- Painless goiter “woody”
- Open biopsy often needed to diagnose
- Associated with focal sclerosis syndromes (retroperitoneal, mediastinal, retroorbital, and sclerosing cholangitis)

Treatment
- Resection for compressive symptoms
- Chemotherapy with Tamoxifen, Methotrexate, or steroids may be effective
- Thyroid hormone only for symptoms of hypothyroidism