

THYROID DISORDERS

Learning objectives

- To define “Hypothyroidism” and “Hyperthyroidism”.
- To identify the underlying causes of hypothyroidism and hyperthyroidism.
- To diagnose and manage hypothyroidism and hyperthyroidism.
- To identify and manage thyroid nodules.

A. HYPOTHYROIDISM

Definition

- **Overt hypothyroidism:** High thyroid-stimulating hormone (TSH) and low free T4 and/or free T3.
- **Primary hypothyroidism:** High TSH and low free T4 (95% of all cases).
- **Secondary hypothyroidism** (central): Low free T4 and a TSH level not appropriately elevated.
- **Subclinical hypothyroidism:** Normal free T4 in the presence of an elevated TSH.

Epidemiology

- Overt hypothyroidism: 0.1 to 2 %.
- Subclinical hypothyroidism: 4 to 10 % in adults with the possibility of higher frequency in elderly women.
- Hypothyroidism is 5 to 8 times more common in women than men.

Causes

- **Chronic autoimmune thyroiditis** (Hashimoto): is the main and most common cause.
- Other causes include:
 - Iatrogenic: Thyroidectomy, Radioiodine therapy or external irradiation.
 - Drugs: thionamides, lithium, amiodarone.
 - Infiltrative diseases : hemochromatosis, sarcoidosis.
 - Transient hypothyroidism: thyroiditis.
 - Congenital thyroid agenesis, dysgenesis, or defects in hormone synthesis.

Medical History

- Typical Symptoms: fatigue, cold intolerance, weight gain, constipation, myalgias, menstrual irregularities.
- Symptoms can be variable and might depend on age at onset, duration and severity of the thyroid hormone deficiency.
- Atypical symptoms are more common in elderly patients.
- Additional information on use of thyrotoxic drugs, previous iodine therapy or previous thyroid surgery need to be gathered.

Physical Exam

- Look for thyroid enlargement (goiter).
- Look for old thyroidectomy scar.
- Other features to look for:
 - Bradycardia
 - Coarse facies
 - Lateral eyebrow thinning
 - Macroglossia
 - Periorbital edema
 - Delayed relaxation phase of deep tendon reflexes
 - Hypothermia
 - Pleural or pericardial effusion.

Diagnostic Tests

- Order **TSH** first; if TSH is high, order **Free T3** and **Free T4**.
- **Antithyroid antibodies** (anti-thyroperoxidase and anti-thyroglobulin): there is no need to measure them routinely in patients with overt primary hypothyroidism, as almost all have chronic autoimmune thyroiditis.
- **Anti-thyroperoxidase (Anti-TPO) antibodies**: may be useful to predict the likelihood of progression to permanent overt hypothyroidism in patients with subclinical hypothyroidism or those with painless (silent) thyroiditis or postpartum thyroiditis.

Management

- Thyroid hormone replacement with **Levothyroxine** (also called L-Thyroxine or LT4) unless:
 - the cause is transient OR
 - reversible .
- Recommended LT4 dose is 1.6 microgram/kilogram (mcg/kg) body weight per day.
- Dose of LT4 usually ranges between 50 and 200 mcg/day.
- Older patients should be started on a lower dose (25 to 50 mcg daily) to avoid arrhythmias.

Follow Up

- Patients start to improve within 2 weeks after treatment initiation.
- TSH is to be measured in 6 weeks after starting treatment and the patient should be evaluated then.
- If the TSH remains above the normal reference range, the dose of LT4 can be increased by 12 to 25 mcg/day. The patient will require a repeat TSH measurement in another 6 weeks.
- After identification of the proper maintenance dose, TSH is to be measured once yearly, or more often if there is recurrence of symptoms.
- An Increase in dosage may be required during pregnancy.

Patient Education

- Advise the patient to take Levothyroxin (LT4) on an empty stomach, ideally an hour before breakfast.
- Advise the patient not take with LT4 other medications that interfere with its absorption (bile acid resins, proton pump inhibitors , calcium carbonate, or ferrous sulfate).

B. HYPERTHYROIDISM

Definition

- **Overt hyperthyroidism** is high Free T3 or Free T4 with suppressed TSH.
- **Subclinical hyperthyroidism** is normal Free T3 and Free T4 with suppressed TSH.

Epidemiology

- Overall prevalence of Hyperthyroidism is 1.3% and it increases to 4-5% in older women.
- Hyperthyroidism is more common in women than men (5:1 ratio):
 - Graves' disease is more common in younger women.
 - Toxic nodular goiter is more common in older women.
- Hyperthyroidism has a higher prevalence in smokers.

Common Causes

- Hyperthyroidism with high uptake on thyroid scintigraphy:
 - Autoimmune thyroid disease: Graves' disease, Hashitoxicosis
 - Autonomous thyroid tissue: Toxic adenoma, Toxic multinodular goiter (MNG)
- Hyperthyroidism with a near absent uptake on thyroid scintigraphy:
 - Subacute granulomatous (de Quervain's) thyroiditis
 - Painless thyroiditis (silent thyroiditis, lymphocytic thyroiditis)
 - Postpartum thyroiditis
 - Amiodarone-induced thyroiditis

Medical History

- Typical symptoms: anxiety, tremors, palpitations, heat intolerance, increased perspiration, weight loss, diarrhea.
- Symptoms can be mild or atypical.
- Elderly patients are more likely to develop cardiovascular complications namely arrhythmias .
- Elderly can also develop "apathetic thyrotoxicosis", in which they have no symptoms except weakness and asthenia.

Physical Exam

- Thyroid Exam: look for palpable nodule or goiter with multiple nodules.
- General Exam:
 - Signs of sympathetic over activity: Tachycardia, tremors, hyperreflexia, high blood pressure.
 - Warm, moist skin, thin, fine hair.
 - Exophthalmos, periorbital and conjunctival edema, limitation of eye movement, and pretibial myxedema, which occur only in patients with Graves' disease.

Diagnostic Tests

- Order **TSH**; if low, ask for **Free T3** and **Free T4**.
- **Thyrotropin receptor autoantibodies (TRAB)** if suspecting Graves disease.
- **Thyroid scintigraphy** (Tc-99m pertechnetate or I-123 scan) is the most useful test to establish cause of hyperthyroidism:
 - If high uptake, autonomy or auto-immune .
 - If low uptake, thyroiditis (subacute, postpartum, amiodarone induced).

Management

- **Beta blockers** are used in moderate to severe hyper-adrenergic symptoms irrespective of the cause of hyperthyroidism.
- Use Propranolol 10-40 mg/dose every 6-12 hours or Atenolol 25 to 50 mg QD, and titrate up the dose as needed, up to 200 mg daily).
- Additional treatment modalities are recommended in Graves disease and toxic adenoma or multinodular goiter.

Medical Treatment in Graves Disease

- Thionamides (Metimazole)
 - Dosage varies depending on the severity of hyperthyroidism:
 - Mild hyperthyroidism (free T4, 23-50 pmol/l): Initial dose is 15 mg/day in 3 divided doses (every 8 hours).
 - Moderate hyperthyroidism (fT4, 51-100 pmol/l): 30-40 mg/day.
 - Severe hyperthyroidism (fT4>100 pmol/l): 60 mg/day.
 - Maintenance: 5-15 mg/day (may be given as a single daily dose in many cases).
- Propylthiouracil (PTU)
 - PTU is the preferred drug during pregnancy.

Additional Management in Graves Disease

- **Radioiodine therapy** : is considered definitive therapy once patients are euthyroid on a thionamide given its lower cost and lower complication rate as compared to surgery (Grade 2B).
- **Surgery** or radioactive iodine (RAI) is preferred over prolonged thionamide therapy for long term remission (Grade 2B).

Surgery in Toxic adenoma or Multinodular goiter

- Compelling indications for surgery are:
 - Symptoms or signs of compression/obstruction
 - A need for rapid return to euthyroidism state
 - Coexisting thyroid cancer
 - very large goiters (>80 g) (Grade 2 C)
- Patients with toxic adenoma/MNG who are to undergo surgery should be treated with an antithyroid drug (methimazole or carbimazole) until they are euthyroid.
- The antithyroid drug should be discontinued on the day of surgery.

Radioactive iodine Therapy in Toxic Adenoma or Multinodular Goiter

- In the absence of surgery indication, Radioactive Iodine (RAI) should be administered (Grade 2C).
- For patients with significant symptoms of hyperthyroidism and in elderly patients with underlying cardiac disease, thionamide (methimazole or carbimazole) should be started first to achieve euthyroidism prior to RAI therapy. Methimazole is then discontinued 3 days prior to RAI.
- After RAI treatment, patients require monitoring for hypothyroidism or persistent or recurrent hyperthyroidism.
- Measure thyroid tests 6 - 8 weeks after RAI treatment and then at 4 - 8 week intervals thereafter, depending upon the results of prior testing and change in thyroid size.

C. THYROID NODULE

Epidemiology

- Life time risk of developing a palpable thyroid nodule is 5-10%.
- Affects more women than men.
- Roughly 5% of thyroid diseases are malignant.

Medical History Elements Suggesting Malignancy

- Age younger than 30 or older than 60 years
- Male sex
- Associated symptoms of dysphasia or odynophagia
- History of neck irradiation
- Prior history of thyroid carcinoma
- Firm, hard or immobile nodule
- Presence of cervical lymphadenopathy
- Rapidly growing nodule

Medical History Elements Suggesting Benign Nodule

- Family history of autoimmune disease (Hashimoto thyroiditis)
- Family history of benign thyroid nodule or goiter
- Presence of thyroid hormonal dysfunction (hypo/hyperthyroidism)
- Pain or tenderness associated with nodule
- Soft, smooth, and mobile nodule

Physical Exam

- Location and size of the nodule
- Solitary or multiple
- Fixed/ movable
- Consistency
- Presence of cervical lymphadenopathy

Imaging Tests

■ **Ultrasound of Thyroid**

- Mandatory in all cases.
- Determines the size and number of thyroid nodules
- Can not reliably distinguish a benign from a malignant nodule

■ **Thyroid Scintigraphy**

- Should be requested if TSH is low.
- It describes a nodule as hot, warm, or cold on the basis of its relative uptake of radioactive isotope.
- Hot nodules are rarely malignant; whereas, 5-8% of warm or cold nodules are malignant.

Laboratory Tests

- **TSH**: to screen for hypothyroidism or hyperthyroidism.
- **FreeT4** and **freeT3** levels if TSH is abnormal.
- **Calcitonin level** measurement to detect medullary Carcinoma is controversial.

Fine Needle Aspirate

- Fine Needle Aspirate (FNA) is the most important and cost-effective step to rule out malignancy in case of thyroid nodule.
- Recommendations for FNA of thyroid nodule depend on the presence of risk factors for thyroid cancer:
 - Head and neck irradiation during childhood
 - Family history of thyroid cancer

Indications for FNA in Patients without Risk Factors for Thyroid Cancer

- Solid hypoechoic nodules >1 cm.
- Solid nodules that are isoechoic or hyperechoic ≥ 1.0 to 1.5 cm.
- Mixed cystic-solid nodules without suspicious features on ultrasound, if ≥ 2.0 cm.
- Spongiform nodules may not require FNA regardless of size, although it may be prudent to biopsy spongiform nodules >2.0 cm.
- Purely cystic nodules do not require a biopsy.

Indications for FNA in Patients with Risk Factors for Thyroid Cancer

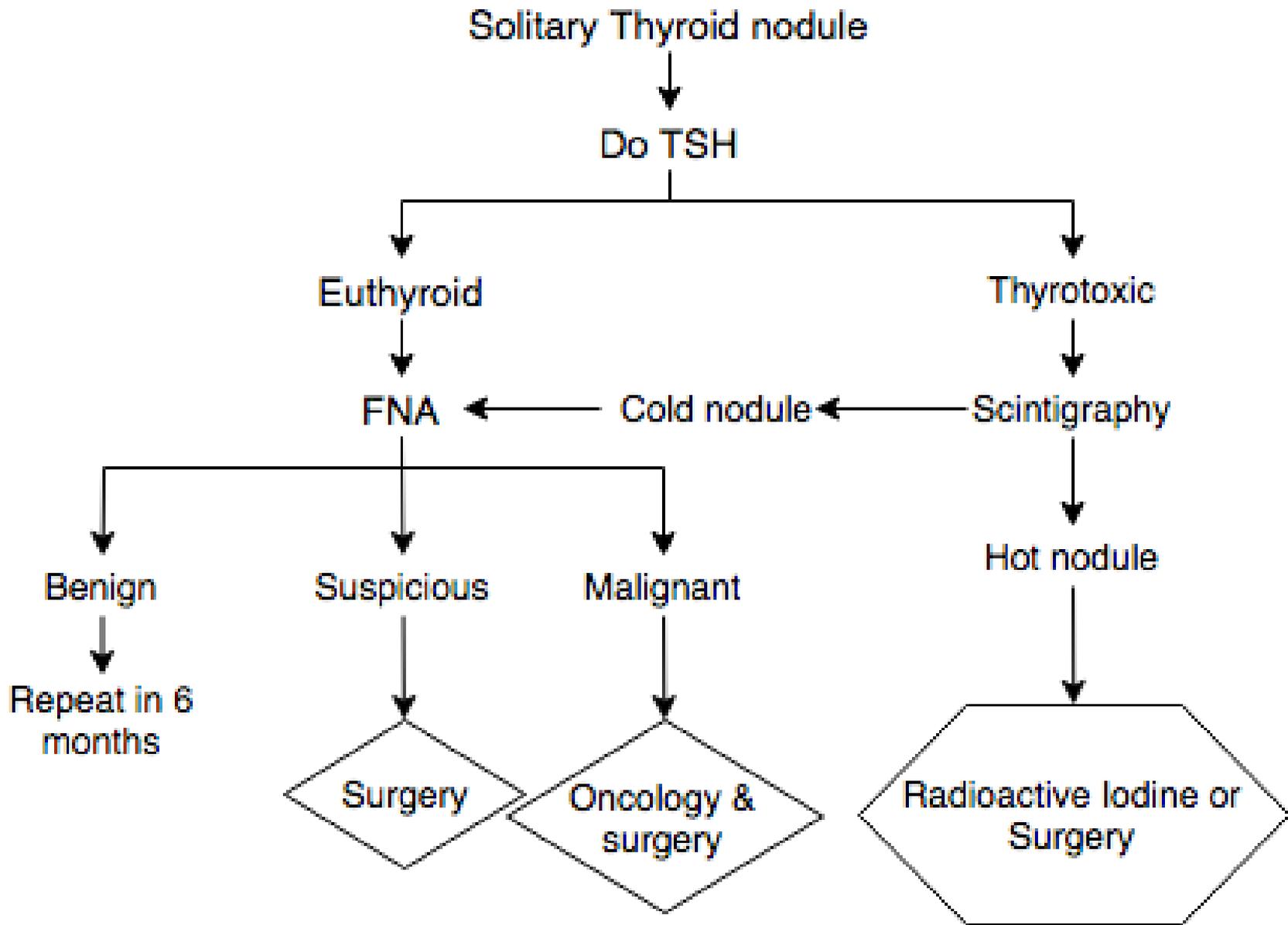
- The American Thyroid Association guidelines recommend ultrasound-guided FNA biopsy for all nodules >5 mm in high-risk patients.
- Subcentimetric nodules are usually biopsied in case of suspicious ultrasonographic features

Management (1)

- Small nodules that are not biopsied need to have a periodic ultrasound to evaluate for increasing size.
 - Do ultrasound initially at 6 to 12 months, then at increasing intervals (at 1-2 year intervals, then 3-5 years), if stable.
- Benign nodules
 - Do not require treatment
 - Periodic ultrasound monitoring recommended
 - Repeat FNA is recommended only in case of substantial growth, change in the echo texture of a nodule, or new symptoms that are attributed to a nodule.

Management (2)

- Follicular lesions of undetermined significance (includes nodules with atypical cells or nodules with both macro-follicular and micro-follicular features)
 - Repeat FNA after 3 to 6 months.
 - Surgical resection should be considered if:
 - Repeat aspirates continue to show atypical cells (Grade 2C).
 - COLD nodules(Grade 2B).
 - Cytology suggesting cancer or suspicious for cancer.



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