Thyrotoxicosis

Department of Endocrinology, Diabetes and Isotope Therapy

Wroclaw Medical University

Hyperthyroidism

Excessive production of the thyroid hormones.

Thyreotoxicosis

Clinical manifestation of excessive quantities of the thyroid hormones, regardless of the cause of this condition.

- one of the most frequent hormonal dysfunction - 2% of adult population
- more common in women, rare in children

Thyrotoxicosis - causes

- Excessive production of the thyroid hormones

- Graves disease
- Toxic nodular goiter:
  - ✓solitary toxic thyroid adenoma
  - ✓multinodular toxic goiter

Thyrotoxicosis - causes

- Excessive production of the thyroid hormones

rarely

- thyroid cancer (usually follicular)
- familial/sporadic activating TSH receptor mutation
- TSH-producing pituitary adenoma
- iodine-induced hyperthyroidism
- pregnancy-associated transient hyperthyroidism
- familial gestational hyperthyroidism
- trophoblastic disease (choriocarcinoma, hydatidiform mole)
- struma ovarii

Thyrotoxicosis - causes

- Disorders associated with excessive quantities of the thyroid hormones (without overproduction)

- thyroiditis
- ✓ subacute
- ✓ postpartum
- ✓ chronic autoimmune - Hashitoxicosis
- ✓ drug-induced

- iatrogenic overreplacement with thyroid hormone
- excessive self-administered thyroid medication
- food and supplements containing excessive thyroid hormone

Graves disease

- autoimmune disorder

<u>antibodies:</u>

- ✓ against TSH receptor (90%) – III classes: thyroid-stimulating antibiodies(anti-TSHR), thyroid-blocking antibodies (TBAb), TSH binding inhibitory immunoglobulins (TBII)
- ✓ anti-TPO – 80%
- ✓ anti-TG – 50%

- more frequent in women (8x), 30-60 yrs., peak incidence - 20-40 yrs.
- more frequently in patients with other autoimmune diseases

Graves disaese

- risk factors

- genetic (80%) – Graves disease is more frequent in monozygotic twins and relatives; HLA DQA1*0501, DRB1*03, cytotoxic T-lymphocyte-associated protein 4 (CTLA4), polimorphisms of the TSH gene

- environmental risk factors (20%) – infections (viral/bacterial - *Yersinia enterocolitica*), stress, nicotinism, iodine-rich diet, immunomodulating agents

Graves disease – clinical manifestations

- **thyroid dysfunction** – depending on the type of antibodies
  - thyrotoxicosis – most frequently
  - euthyreosis
  - hypothyrosis – rarely

- **goiter (70%)**
- **ophtalmopathy (25-30%)**
- **pretibial edema (2-3%)**
- **acropachy (<1%)**

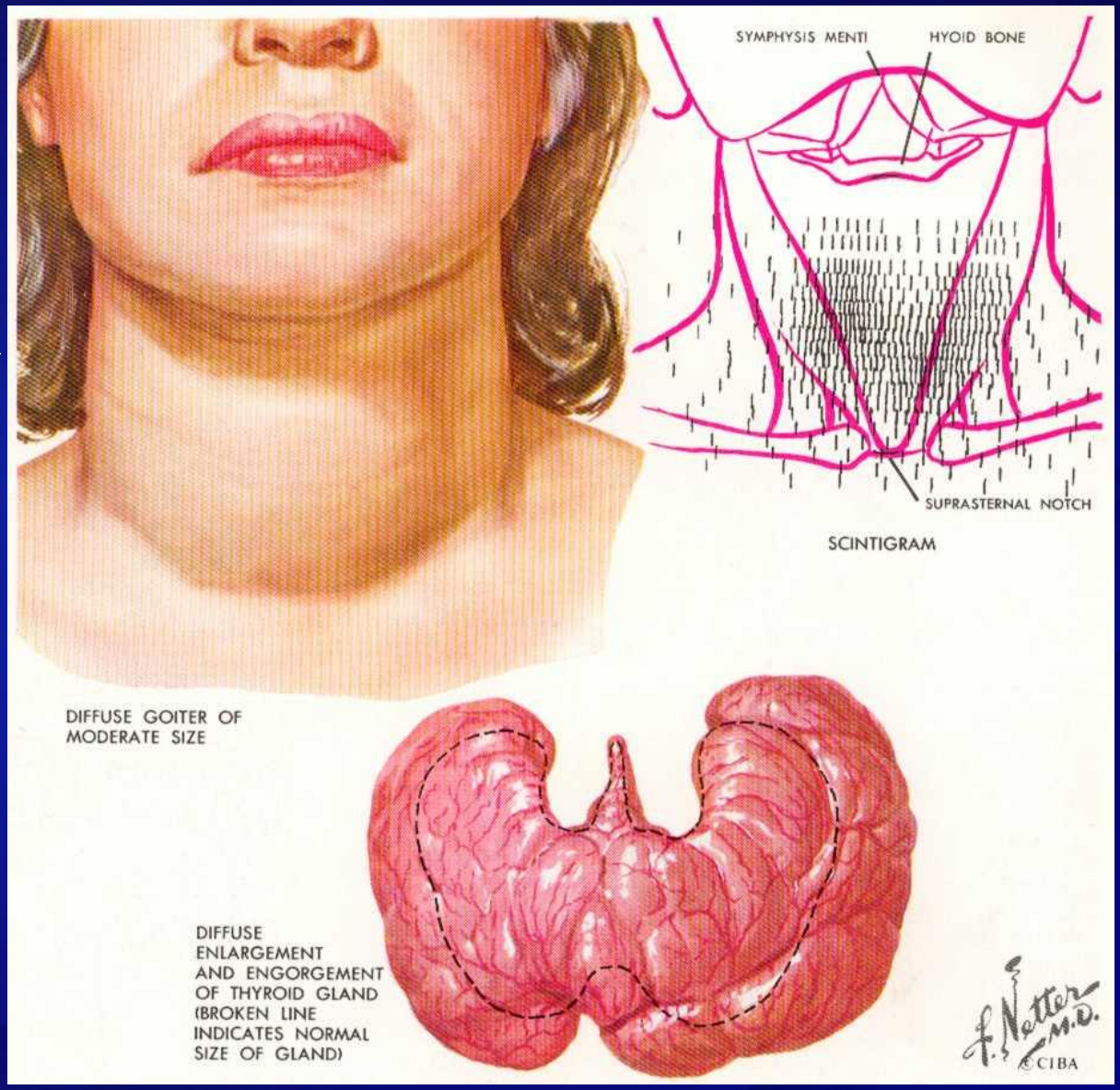
Graves disease – atypical forms

- elderly – atrial fibrillation, exacerbation of ischemic cardiac disease/heart failure)
- apatic (after 60 yrs., rarely) – severe depression, weight loss
- miastenic

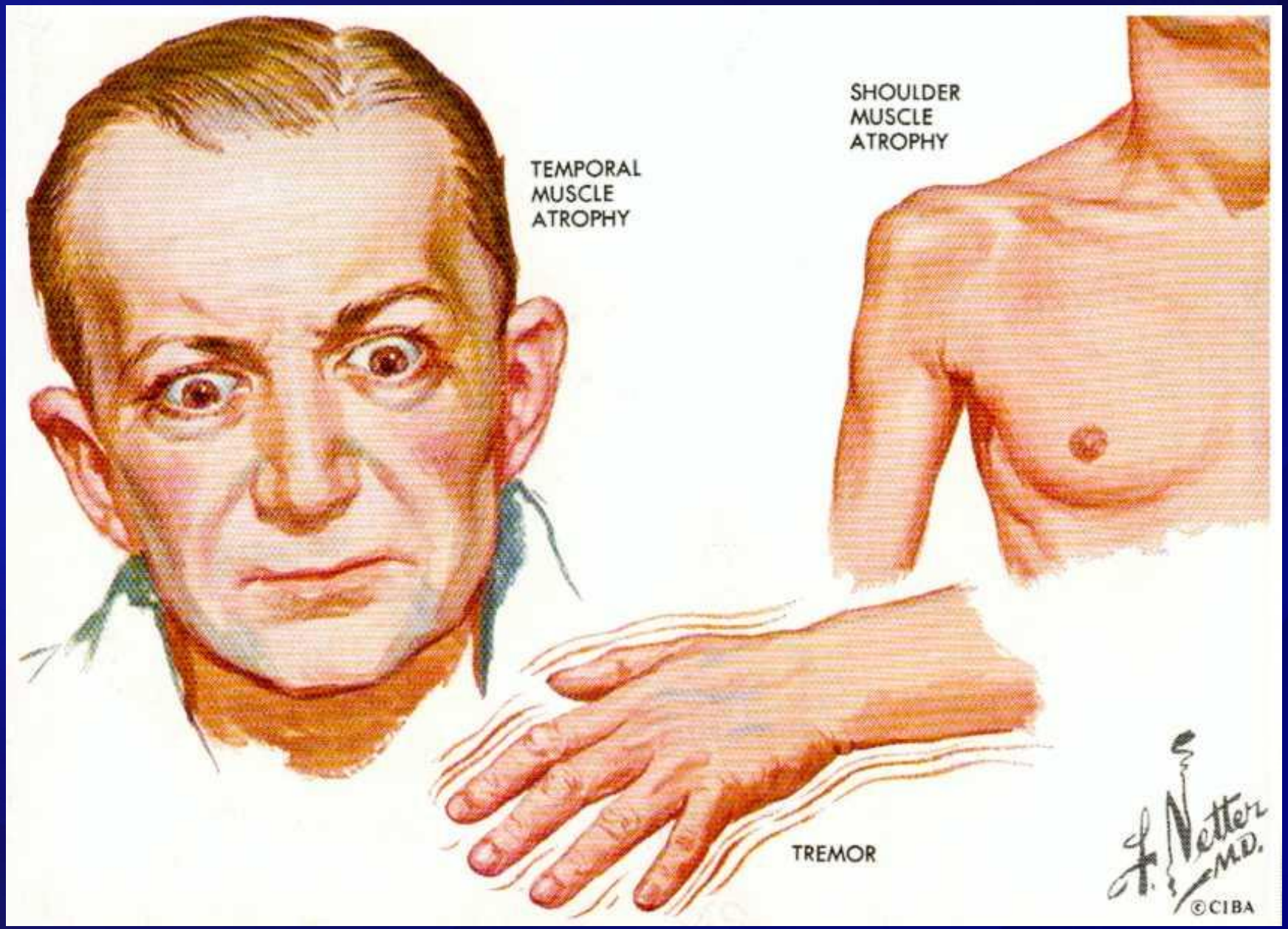
Graves disease

Diffuse goiter

- ✓ usually symmetrical
- ✓ soft to firm consistency
- ✓ thrill over the upper and lower poles
- ✓ rarely – thyroid gland is not enlarged (more frequently in men)



Graves disease



Orbitopathy

- chronic autoimmune inflammation of intraorbital tissues, usually associated with thyrotoxicosis (80%), rarely during euthyreosis

- pathogenesis

- autoimmune reaction of anti-TSH receptor antibodies with intraorbital conective tissue

Orbitopathy – pathogenesis

- TSH receptor (TSHR) is expressed primarily in the thyroid but is also expressed in adipocytes, and fibroblasts
- TSHR antibodies and activated T cells play an important role in the pathogenesis of Graves' orbitopathy by activating retroocular fibroblast and adipocyte TSHR receptors and initiating a retro-orbital inflammation
- the volume of both the extraocular muscles and retroocular connective tissue is increased, due to fibroblast proliferation, inflammation, and the accumulation of hydrophilic glycosaminoglycans (GAG)
- the accumulation of hydrophilic GAG in turn leads to fluid accumulation, muscle swelling and an increase in pressure within the orbit
- these changes displace the eyeball forward, leading to extraocular muscle dysfunction

Orbitopathy

- Risk/aggravating factors

- environmental – smoking!!!
- smoking is associated with an increase in the connective tissue volume of the orbit but not the extraocular muscle volumes. How this might occur is not known, but direct toxic effects of smoke on the inflamed eyes are likely, and immunologic changes have been described in smokers that could affect the autoimmune proces. In vitro data suggest that cigarette smoke stimulates GAG production and adipogenesis in a dose-dependent manner.

- poorly controlled thyroid function
- radioiodine therapy

- unknown genetic risk factors

Orbitopathy – signs and symptoms

- ✓ a gritty or foreign object sensation in the eyes
- ✓ excessive tearing (especially during exposure to cold air, wind, or bright lights)
- ✓ blurred vision
- ✓ diplopia
- ✓ eye or retroocular pain or discomfort
- ✓ redness of the eyelids and conjuctiva
- ✓ swelling of the eyelids and conjuctiva
- ✓ decrease in eye muscle motility
- ✓ exophtalmos (proptosis)
- ✓ corneal ulceration
- ✓ decreased visual acuity
- ✓ glaucoma caused by exophtalmos

Orbitopathy – differential diagnosis

- **in case of unilateral exophtalmos it's necessary to exclude:**
  - orbital tumors, inculding metastatic tumors to the orbit
  - caroticocavernous fistula
  - sarcoidosis
  - infection
  - Wegener's granulomatosis
  - non-Hodgkin lymphoma

Orbitopathy – severity and activity measures

- disease activity is commonly assessed using a seven-point clinical activity score (CAS)
- patients with a score of 3 or more are classified as having active disease and are therefore more likely to respond to immunomodulatory therapy, such as corticosteroids

TABLE 12.8 Clinical Assessment of the Patient With Graves Orbitopathy

SEVERITY MEASURES (USING THE MNEMONIC NO SPECS)

NO SPECS Class	Item	Method
0. No signs or symptoms		
1. Only signs, no symptoms	Lid aperture	With ruler in midline in mm
2. Soft tissue involvement	Eyelid and conjunctiva swelling and redness	Inspection, color pictures[a]
3. Proptosis	Exophthalmos	Hertel in mm
4. Extraocular muscle involvement	Eye muscle motility Diplopia	Impaired elevation, abduction Subjective grading[b]
5. Corneal involvement	Keratitis, ulcer	Fluoresceine
6. Sight loss due to optic nerve involvement	Dysthyroid optic neuropathy (DON)	Visual acuity, color vision, visual fields, optic disc

ACTIVITY MEASURES (USING THE CLINICAL ACTIVITY SCORE [CAS])

Inflammatory Sign	Item	Score
Pain	Spontaneous retrobulbar pain	1
	Pain on up gaze, side gaze, or down gaze	1
Redness	Redness of the eyelids	1
	Redness of the conjunctiva	1
Swelling	Swelling of the eyelids	1
	Swelling of the caruncle and/or plica	1
	Chemosis	1
Maximum CAS score (assessed momently)		*7*
Impaired function	Increase in proptosis ≥2 mm in 1–3 months	1
	Decrease of ≥8° in eye muscle motility in any direction in 1–3 months	1
	Decrease in visual acuity of more than one line on the Snellen chart (using pinhole) in 1–3 months	1
Maximum CAS score (assessed over time)		*10*

[a]Color atlas in Dickinson AJ, Perros P. Controversies in the clinical evaluation of active thyroid-associated orbitopathy: use of a detailed protocol with comparative photographs for objective assessment. *Clin Endocrinol (Oxf)*. 2001;55:283–303.

[b]Intermittent diplopia – at awakening or when tired; inconstant diplopia – at extremes of gaze; constant diplopia – in primary or reading position.

Graves' orbitopathy severity assessment [1-4]

Grade*	Lid retraction	Soft tissues	Proptosis ¶	Diplopia	Corneal exposure	Optic nerve status
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	≥2 mm	Moderate involvement	≥3 mm	Inconstant	Mild	Normal
Severe	≥2 mm	Severe involvement	≥3 mm	Constant	Mild	Normal
Sight threatening	–	–	–	–	Severe	Compression
Upper limits of normal						
African American	F/M = 23/24 mm					
White	F/M = 19/21 mm					
Asian	F/M = 16/17 mm (Thai) or 18.6 mm (Chinese)					

F: female; M: male; GO: Graves' orbitopathy.
* Mild GO: patients whose features of GO have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment. Moderate-to-severe GO: patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Sight-threatening GO: patients with dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.
¶ Proptosis refers to the variation compared with the upper limit of normal for each race/sex or the patient's baseline, if available.

References:

1. *de Juan E Jr, Hurley DP, Sapira JD. Racial differences in normal values of proptosis. Arch Intern Med 1980; 140:1230.*
2. *Sarinnapakorn V, Sridama V, Sunthornthepvarakul T. Proptosis in normal Thai samples and thyroid patients. J Med Assoc Thai 2007; 90:679.*
3. *Tsai CC, Kau HC, Kao SC, Hsu WM. Exophthalmos of patients with Graves' disease in Chinese of Taiwan. Eye (Lond) 2006; 20:569.*
4. *Bartalena L, Baldeschi L, Dickinson AJ, et al. Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid 2008; 18:333.*

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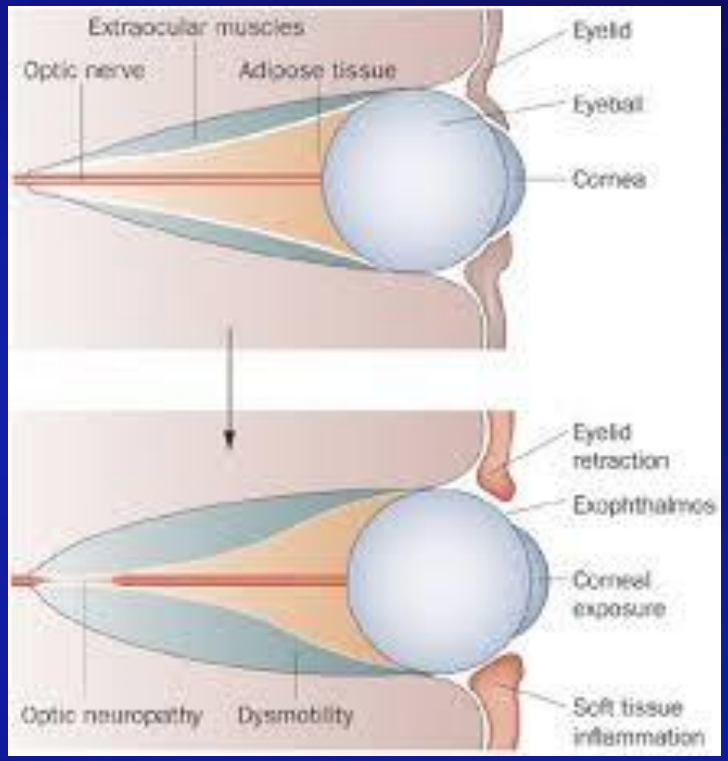
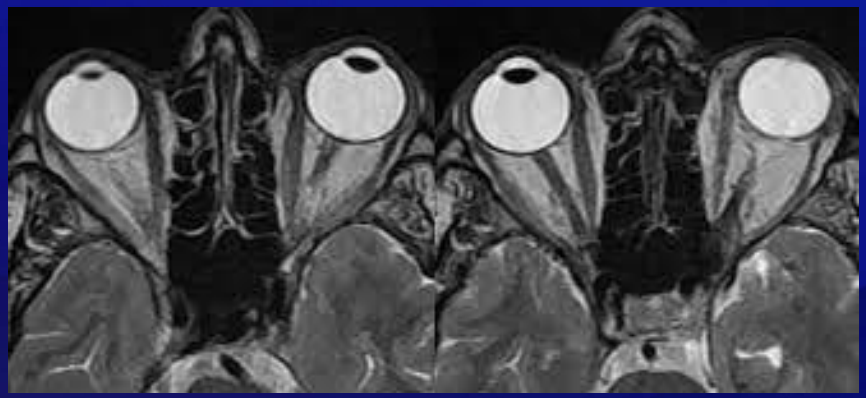
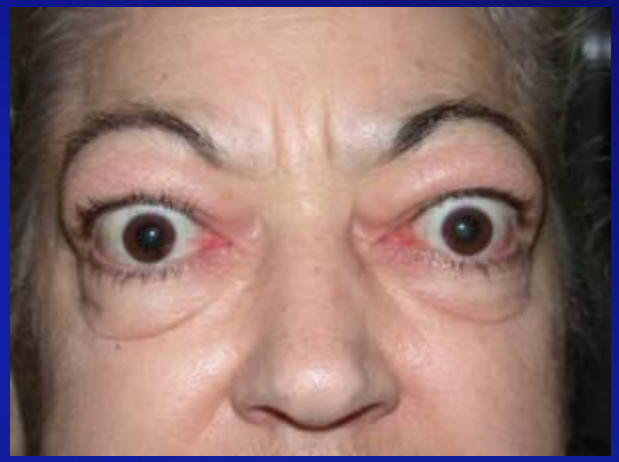
Orbitopathy





Orbitopathy



Graves' disease: complications, www.endotext.org

Orbitopathy - treatment

- <u>treatment of patients with Graves' orbitopathy includes:</u>

✓ reversal of hyperthyroidism, if present
✓ monitoring for and prompt treatment of hypothyroidism, occurring as a consequence of treating hyperthyroidism
✓ cessation of smoking
✓ local measures to reduce ocular surface irritation:
  - artificial tears
  - raising the head of the bed at night
  - dark glasses
  - lubricants

Orbitopathy - treatment

- <u>treatment of inflammation and swelling – in case of active orbitopathy:</u>

- glucocorticoids intravenously – methylprednisolone 500 mg once weekly for weeks 1-6, then 250 mg once weekly for weeks 7-12 – cumulative dose 4.5 gover 12 weeks

- if high-dose glucocorticoid therapy is contraindicated, cannot be tolerated, or is ineffective, options include other medical therapies, external orbital radiation, or orbital decompression surgery

Orbitopathy - treatment

- sight-threatening Graves' orbitopathy may occur in 3 to 5% of patients with Graves' disease

- threatened loss of vision, often preceded by loss of color vision, is a **medical emergency -** such a patient should receive immediate glucocorticoid therapy, and should be hospitalized for urgent orbital decompression surgery

Orbitopathy - treatment

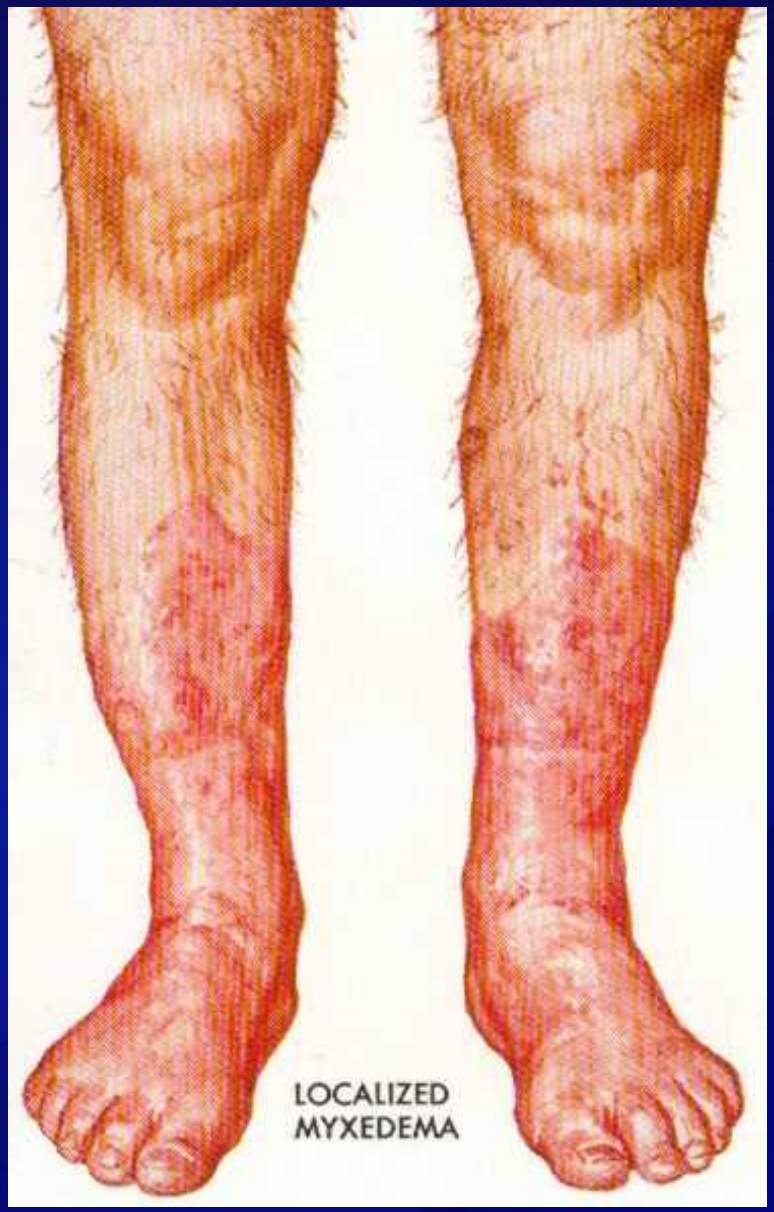
- **orbital decompression surgery - indications:**

- optic neuropathy caused by enlarged extraocular muscles not responsive to high-dose corticosteroids
- severe orbital inflammation
- excessive proptosis leading to keratitis, or corneal ulceration
- progressive orbitopathy not responding to other measures
- the orbit may be decompressed by removing the lateral wall, the roof, or the medial wall and the floor
- **diplopia usually does not improve and may worsen, so that eye muscle surgery is almost always needed later**

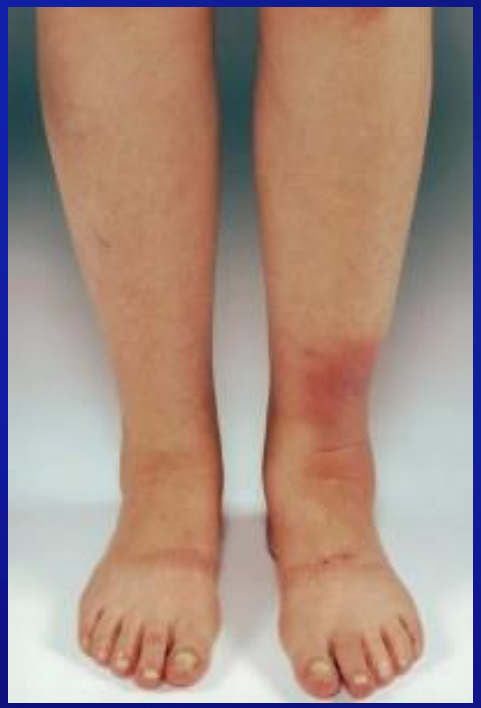
Pretibial myxedema (thyroid dermopathy)

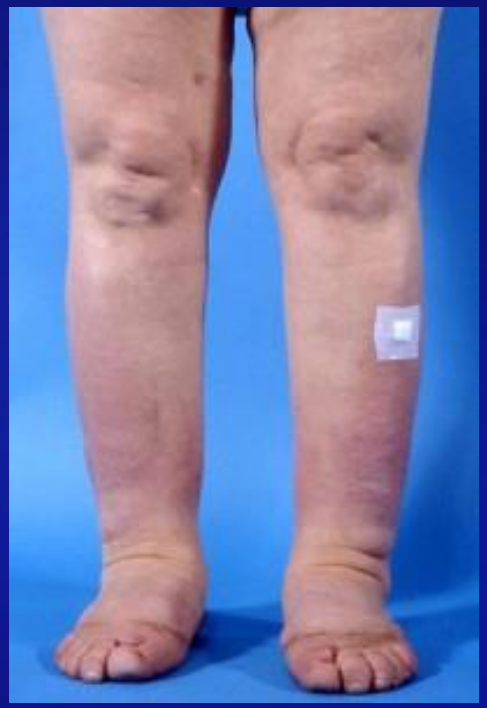
- ✓ rare manifestation of Graves disease
- ✓ bilateral, asymmetric, nonpitting thickening of the skin, violaceous or slightly pigmented (yellow-brown), orange-peel appearance
- ✓ usually asymptomatic but may be pruritic or painful
- ✓ the most frequent location – over the lower legs – especially the pretibial ares or the dorsum of the foot
- ✓ rarely (<1%) – fingers, elbows, hands, arms

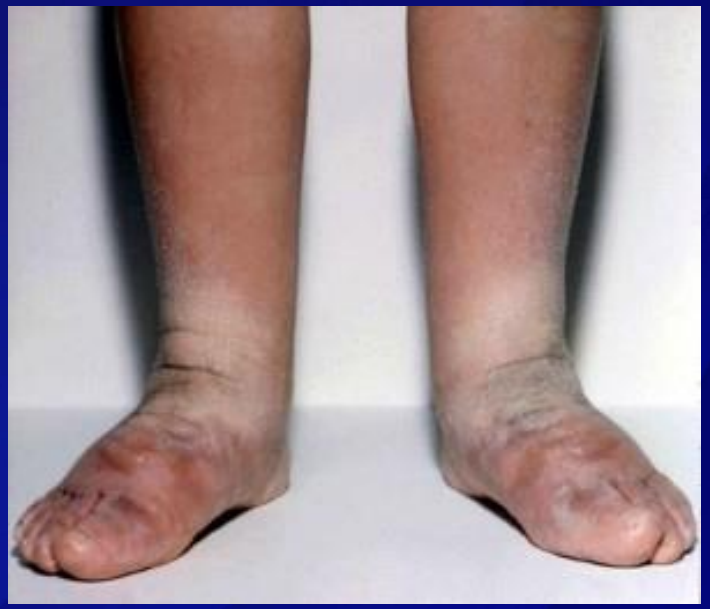
- ✓ treatment – glucocorticoids – topical (ointment), in severe cases - intravenous



Pretibial myxedema







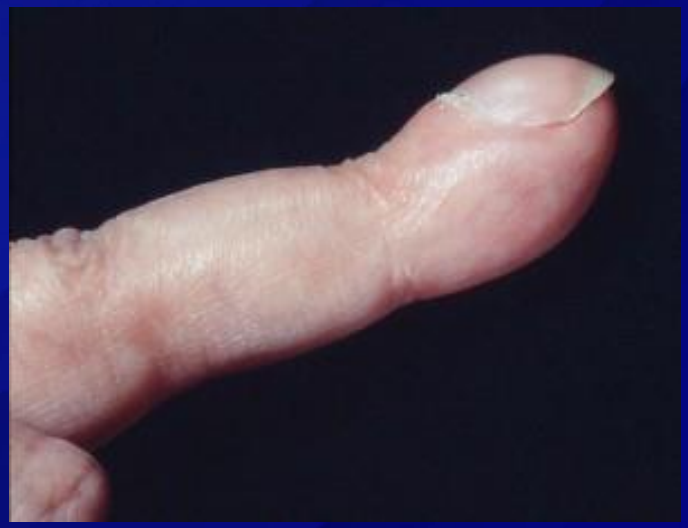
Dr Vahab Fatourechi, Mayo Clinic, www.endotext.org

- Thyroid acropathy

✓ rare manifestation of Graves' disease

✓ digital clubbing, soft-tissue swelling of the hands and feet, and periosteal reaction with new bone formation

✓ it is almost always associated with thyroid dermopathy and exophthalmos



Nodular goiter
Toxic solitary adenoma

- single, autonomous adenoma – 30-40%
- multiple toxic nodules – 60%
- spontanic remission – very rare

Toxic multinodular goiter
Solitary toxic adenoma

- The most frequent cause of hyperthyroidism on iodine deplete areas

- after 60 yrs., more common in women

❖symptoms of obstruction – in very large and longstanding goiters (especially substernal goiters):

✓ compression of the trachea

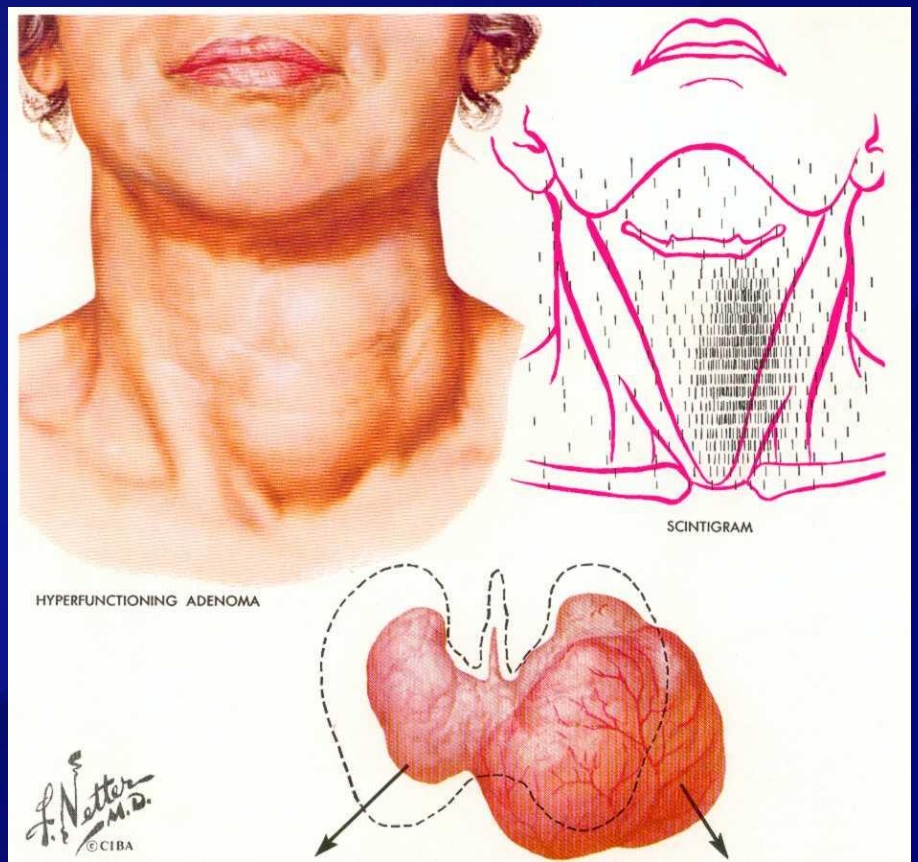
✓ dyspnea, wheezing, stridor

✓ hoarseness

✓ Horner's syndrome due to compression of the cervical sympathetic chain

✓ jugular vein compression

✓ the superior vena cava syndrome



Thyroid carcinoma – very rare cause of thyrotoxicosis

- usually follicular carcinoma

- pathogenesis:

✓ excessive production of thyroid hormones by large tumor/functional metastasis caused by autonomic function, or stimulation by anti-TSHR antibodies

✓ destruction of thyroid nodules→transient thyrotoxicosis

✓ worst prognosis in case of coexistence of thyroid carcinoma with Graves disease

Transient thyrotoxicosis

- Thyroiditis with destruction of thyroid parenchyma:
  - subacute (Quervaine's thyroiditis)
  - post-partum
  - painless (silent)
- Hashitoxicosis – transient thyrotoxicosis in the early phase of Hashimoto disease

Drug-induced thyrotoxicosis

- Amiodarone

✓ type I – excessive quantity of iodine → excessive production of thyroid hormones in patients with Graves disease/adenoma/multinodular goiter

✓ type II – destructine of previously normal thyroid gland

✓ type III – mixed type: overproduction of thyroid hormones + destruction of thyroid gland

Tyrotoxicosis – signs and symptoms

- ✓ nervoussness, agitation
- ✓ depression, emotional lability
- ✓ insomnia
- ✓ fine tremor of hands
- ✓ weight loss despite a normal or increased appetite
- ✓ diarrhea
- ✓ heat intolerance, sweating
- ✓ generalized weakness
- ✓ increased heart rate, systolic hypertension, worsening of previously diagnosed congestive heart failure

Tyrotoxicosis – signs and symptoms

- eyes: stare, lid lag in all patients due to sympathetic overactivity, orbitopathy due to autoimmune inflammation in Graves disease
- skin: warm, moist, vitiligo and alopecia areata in case of autoimmune diseases, onycholysis (loosening of the nails from the nail bad), hyperpigmentation, pretibial myxedema in Graves disease
- bones: secondary osteoporosis (thyroid hoemones stimulate bone resorption)

Tyrotoxicosis – signs and symptoms

- gastrointestinal: hyperphagia, increased gut motility, diarrhea
- neurologic manifestation: muscle weakness, decrease muscle mass, increased tendon reflexes, tremor

Tyrotoxicosis – signs and symptoms

- Thyroid gland

- ✓ symmetrically enlarged, smooth, form consistency, audible thrill: Graves disease
- ✓ single or multiple nodules, enlarged thyroid gland (usually asymmetrical): – multinodular toxic goiter/toxic adenoma
- ✓ not enlarged – rarely in Graves disease (usually in men), substernal goiter
- ✓ partial enlargement of thyroid gland, pain or discomfort during palpation – subacute thyroiditis

Tyrotoxicosis – signs and symptoms

- Cardiovascular manifestation

✓ atrial fibrillation, ventricular extrasystoles
✓ atrio-ventricular block – first-degree
✓ sinus tachycardia
✓ increased left ventricular mass index
✓ mitral valve prolapse
✓ high blood pressure amplitude
✓ pulmonary hypertension
✓ mitral regurgitation

Tyrotoxicosis – signs and symptoms in geriatric patients

- hyperthyroidism in older patients may be apathetic, rather than having hyperactivity, tremor, and other symptoms of sympathetic overactivity, however, two-thirds of such patients have symptoms similar to those in younger patients

- Thyreocardiac syndrome

1. heart arrhythmias – sinus tachycardia, atrial fibrillation, ventricular extrasystoles

2. worsening of ischemic heart disease

3. Congestive heart failure (resistant to pharmacotherapy)

Tyrotoxicosis – laboratory tests

↓TSH, fT4/fT3 N = subclinical hyperthyroidism

↓TSH, ↑ fT4 i/lub fT3 = primary hyperthyroidism

↑TSH, ↑ fT4, ↑/norma fT3 = secondary (central) hyperthyroidism

- <u>in Graves disease</u>

✓ TRAB > 90% patients
✓ antyTPO - 70%
✓ antyTG- 20-30%

Tyrotoxicosis – laboratory tests

- biochemistry

- ✓ ↓total cholesterol
- ✓ ↑fasting glucose/impaired results of OGTT
- ✓ ↓leukocytes/granulocyty
- ✓ microcytic/macrocytic anemia
- ✓ ↑aspat/Alat
- ✓ ↑CPK
- ✓ ↑bilirubin
- ✓ ↑calcium

Tyreotoxicosis – imaging

- Thyroid ultrasound

- ✓ Graves disease: symmetrical/asymmetrical enlargment of thyroid gland, heterogenous echogenicity, ↓hypoechogenic structure, ↑vascularity
- ✓ toxic adenoma/toxic multinodular goiter – nodules within thyroid gland
- ✓ subacute thyroiditis – symmetrical/asymmetrical thyroid gland enlargement, hypoechogenic lesions, ↓vascularity
- ✓ Hashitoxicosis – enlarged thyroid gland, ↓echogenicity

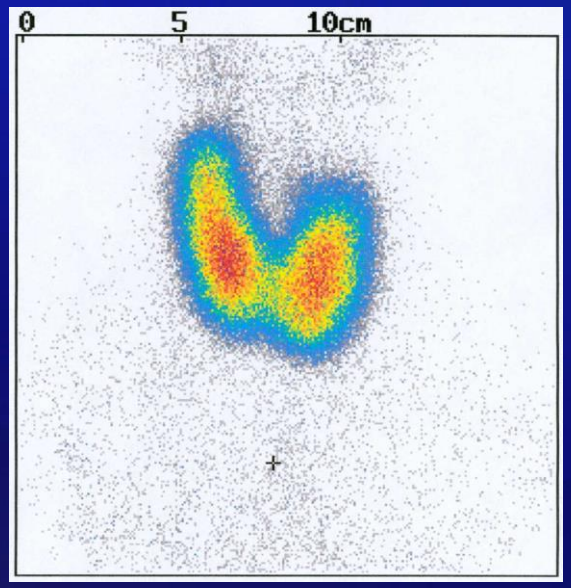
- chest and neck x-ray – in case of substernal or very large goiter

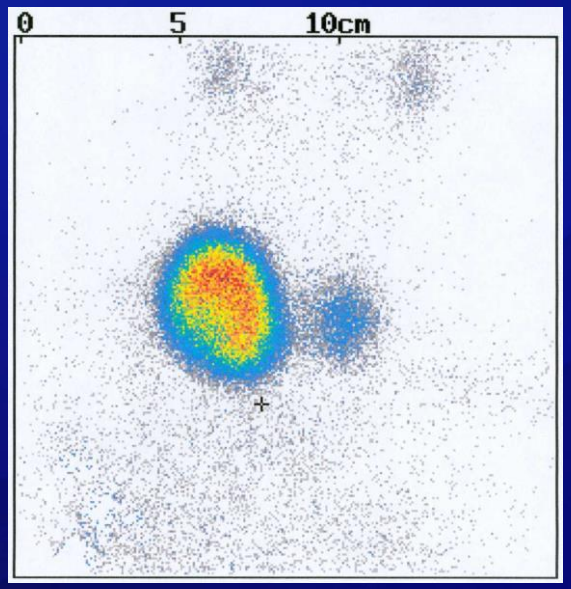
Tyrotoxicosis – imaging

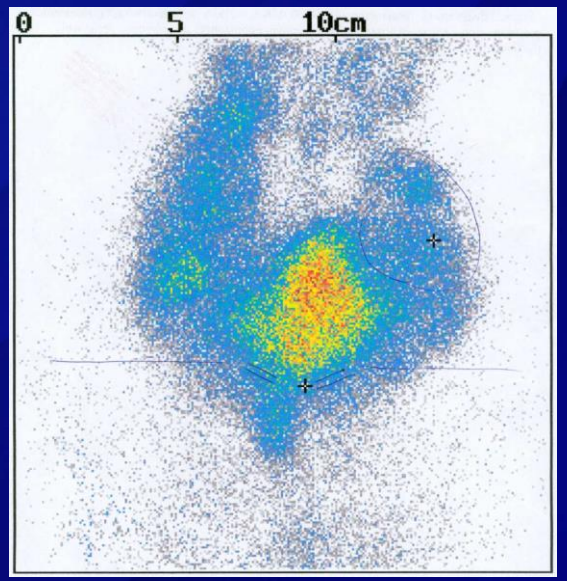
- Scintigraphy

✓ Graves disease – not necessary
✓ toxic adenoma – hot nodule
✓ toxic multinodular goiter – multiple hot nodules

- FNA – indicated in case of nodular goiter to exclude thyroid carcinoma (especially cold nodules), also in case of coexistence of Graves disease with multinodular goiter







Tyrotoxicosis - treatment

Graves disease

options:

- ✓ anti-thyroid drugs (thionamides)
- ✓ radioiodine (I131 isotope)
- ✓ thyroidectomy

- anti-thyroid drugs
- ✓ longstanding treatment (at least 12-18 months)
- ✓ inhibition of thyroid hormones production/release (propylthiouracil (PTU) – additional effect – inhibition of T4 to T3 conversion)
- ✓ PTU – hepatotoxic – could be used only during I trimester of pregnancy (safer than tiamazole during organogenesis)

Tyreotoksykoza - treatment

- anti-thyroid drugs – thionamides

✓ side effects

○ skin allergy (pruritus, rash, urticaria), gastrointestinal signs (nausea, vomiting)

○ **serious adverse effects, indication for prompt discontiunation of therapy:**

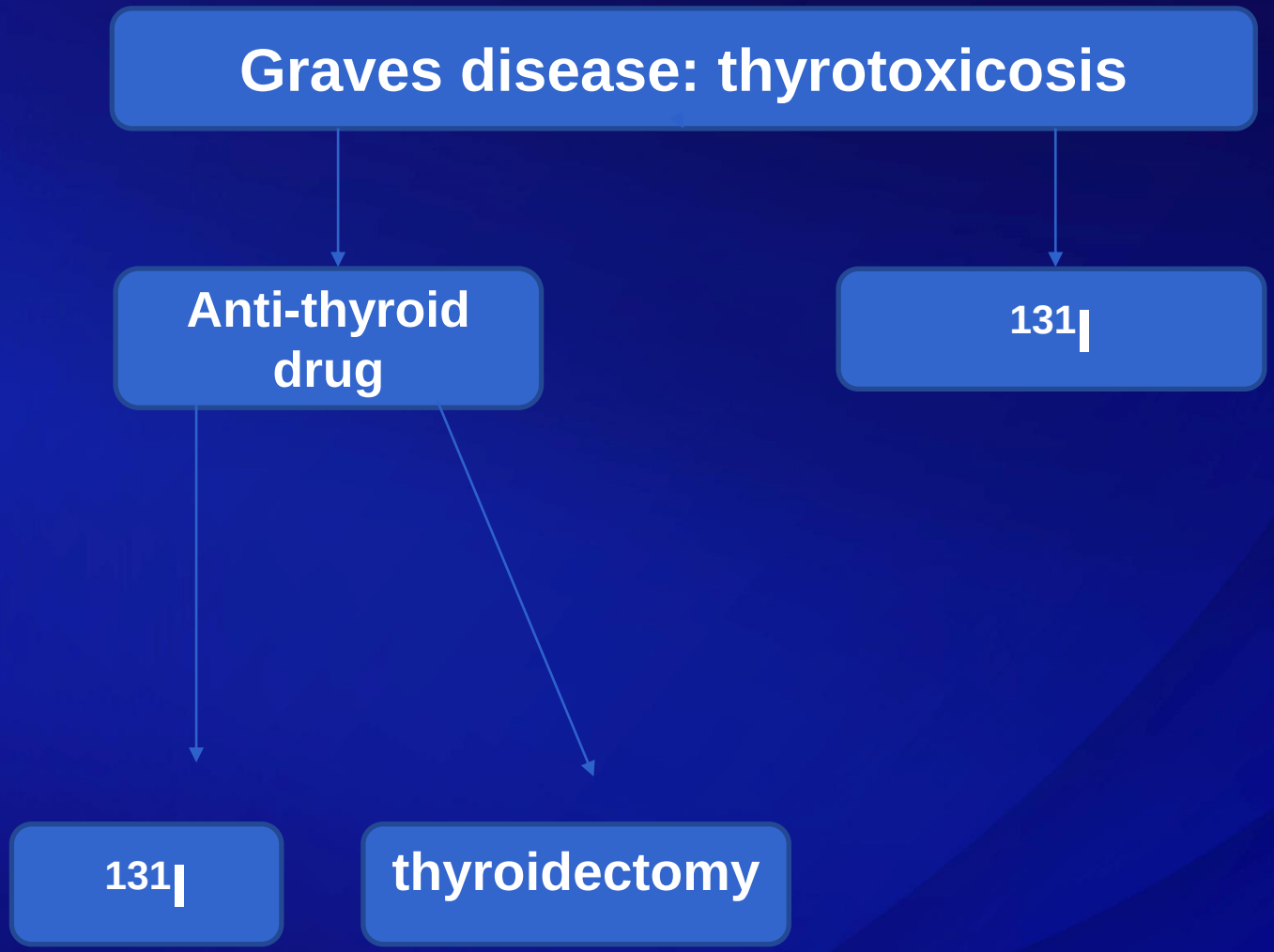
✓ agranulocytosis

✓ hepatotoxicity (PTU can cause fulminant hepatic necrosis!)

✓ ANCA-positive vasculitis (usually after PTU)

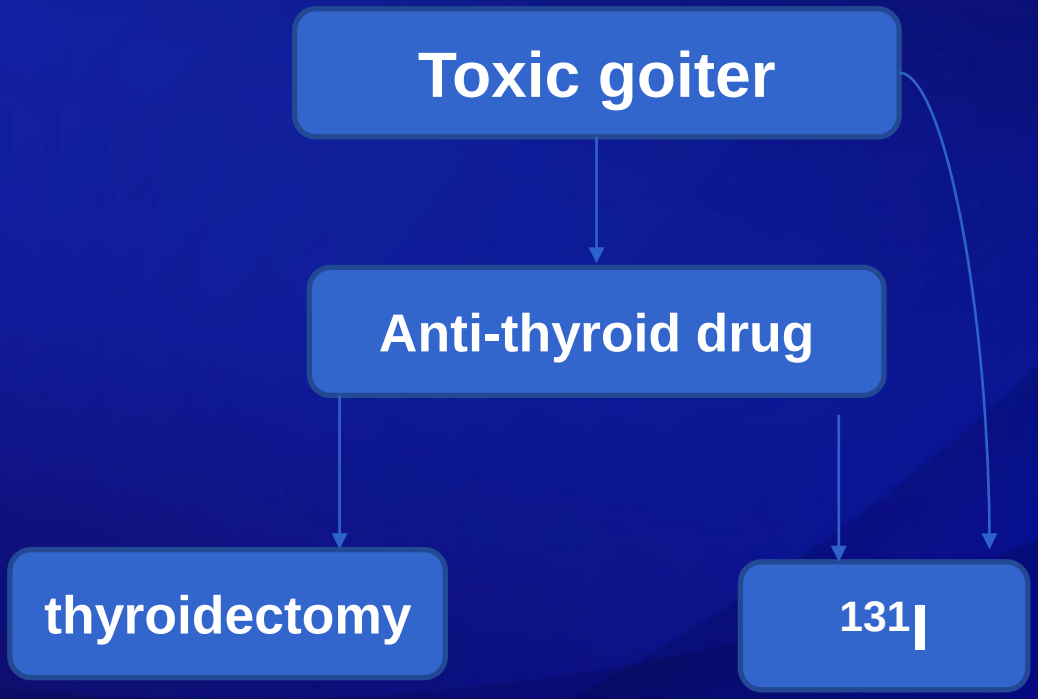
Caution! Prompt medical consultation + blood count is necessary in case of fever, sore throat or other signs and symptoms of infection!

Tyrotoxicosis – treatment – Graves disease



Thyrotoxicosis – toxic multinodular goiter - treatment

- aim – elimination of autonomous thyroid tissue
- Thyroidectomy after preparation to surgery (patient have to be euthyroid, usually it is achieved after thionamides), radioiodine therapy



Tyrotoxicosis - treatment

- radioiodine (I131)

- ✓ β radiation
- ✓ extensive thyroid tissue damage, fibrosis → decrease of active thyroid tissue
- ✓ effectiveness – 70-90% in case of Graves disease, 60-70% in case of toxic multinidular goiter
- ✓ reduction in thyroid size
- ✓ 20% of patients – retreatment is needed

Tyrotoxicosis - treatment

- radioiodine – indications in Graves disease

- ✓ recurrences of thyrotoxicosis after pharmacotherapy
- ✓ major adverse reactions to thionamides
- ✓ contraindications for surgery or increased surgical risk
- ✓ previous neck surgery or irradiation
- ✓ elderly with comorbidities

Tyrotoxicosis - treatment

- radioiodine – indications in case toxic multinodular goiter

- ✓ contraindications for surgery or increased surgical risk
- ✓ lack of acceptance for surgery
- ✓ recurrence of thyrotoxicosis after surgery

Tyrotoxicosis - treatment

- radioiodine - contraindications

✓ **pregnancy and breastfeeding !!!**

✓ cancer of thyroid gland

✓ age < 10 rż.

✓ lack of acceptance

✓ low radioiodine uptake

✓ moderate to severe, active orbitopathy

✓ very large goiter

Tyrotoxicosis - treatment

- surgery - thyroidectomy

Indications in case of Graves disease

- ✓ absent or very low radioiodine uptake
- ✓ lack of acceptance of radioiodine treatment
- ✓ carcinoma of thyroid gland
- ✓ severe, active orbitopathy
- ✓ lack of permanent euthyroidism despite pharmacotherapy (thionamides or I131)
- ✓ large goiter with compression on surrounding structures

Indications in case of toxic multinodular goiter

- ✓ very large goiter (>60 ml)
- ✓ goiter with compression on surrounding structures
- ✓ suspicion of thyroid carcinoma
- ✓ contraindications to ^{131}I, lack of acceptance of I131
- ✓ contraindications/inefficiency of pharmacotherapy

Thyroid storm

- thyroid storm is a rare, life-threatening condition characterized by severe clinical manifestations of thyrotoxicosis
- it may be precipitated by an acute event such as thyroid or nonthyroidal surgery, trauma, infection, an acute iodine load, or parturition

- <u>risk factors</u>

✓ infection
✓ trauma, thyroid or not thyroidal surgery
✓ parturition
✓ irregular use or sudden discontinuation of thionamides
✓ acute iodine load
✓ radioiodine therapy in case of severe thyroroxicosis
✓ drugs - salicylates

Thyroid storm

- ✓ sudden exaggeration of the usual symptoms of hyperthyroidism

- signs and symptoms
- ✓ tachycardia, cardiac arrhythmia, cardiovascular collapse
- ✓ fever
- ✓ excessive sweating
- ✓ agitation, anxiety, delirium, psychosis, stupor, coma
- ✓ severe nausea, vomiting
- ✓ jaundice
- ✓ **the degree of hyperthyroidism (elevation of T4 and/or T3 and suppression of TSH) in patients with thyroid storm is, in general, comparable with that in patients with uncomplicated overt hyperthyroidism**
- ✓ **thus, the degree of hyperthyroidism is not a criterion for diagnosing thyroid storm !!!**

Thyroid storm - treatment

- Intensive Care Unit

- aims of therapy

✓ inhibition of synthesis/release of thyroid hormones
✓ inhibition of T4 to T3 conversion
✓ blockade of beta adrenergic receptors
✓ treatment of concommitant diseases
✓ treatment of complications

Thyroid storm - treatment

- **inhibition of T4 and T3 synthesis**: thionamides iv, p.o., per rectum
- **inhibition of T4 and T3 release**: inorganic/organic, lithium carbonate

✓ iodine-induced thyrotoxicosis – natrium/kalium perchlorate

✓ administration of iodine should be delayed for at least one hour **after** thionamide administration to prevent the iodine from being used as substrate for new hormone synthesis in patients with toxic adenoma or toxic multinodular goiter!

Thyroid storm - treatment

- glucocorticoids – inhibition of T4→T3 coversion, antiinflammatory action, treatment of potentially associated limited adrenal reserve
- β- blockers
- plasmapheresis – in case of ineffectivity of other modalities of treatment

- supportive measures
  - ✓ antipyretics
  - ✓ hydratation.iv., treatment of dyselectolitemia
  - ✓ treatment of infection
  - ✓ treatment of heart failure
  - ✓ sedatives/anticonvulsants
  - ✓ prophylaxis of venous thromboembolism