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Харківський національний медичний університет

DISEASES OF THE THYROID GLAND

Tutorial for students and interns

ЗАХВОРЮВАННЯ ЩИТОПОДІБНОЇ ЗАЛОЗИ

Навчальний посібник для студентів та лікарів-інтернів

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Ж 91 DISEASES OF THE THYROID GLAND: tutorial for students and interns. – Kharkiv : KhNMU, 2020. – 105 p.

The textbook covers important issues of the course of internal medicine, including endocrinology - the problems of diagnosis and treatment of thyroid diseases. The textbook is intended for English-speaking students and interns.

Л.В. Журавльова, М.В. Філоненко

Ж 91 ЗАХВОРЮВАННЯ ЩИТОВИДНОЇ ЗАЛОЗИ: навч. посібник для студентів та лікарів-інтернів. – Харків : ХНМУ, 2020. – 105 с.

У навчальному посібнику висвітлені важливі питання курсу внутрішньої медицини, в тому числі ендокринології - проблеми діагностики та лікування захворювань щитоподібної залози. Навчальний посібник призначений для англомовних студентів та лікарів-інтернів.
Навчальний посібник представлено в авторській редакції.

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List of abbreviations

CBC – complete blood count

ESR - erythrocyte sedimentation rate

FNA - fine-needle aspiration

GLUT-4 - glucose transporter-4

IGF-1 - insulin-like growth factor 1

RAIU - radioactive iodine uptake

rhTSH - recombinant human TSH

SNG - sporadic nontoxic goiter

TBG - thyroxine-binding globulin

TFT - thyroid function test

Tg – thyroglobulin

TGF-β - transforming growth factor β

TPO - thyroid peroxidase

TRH - thyrotropin-releasing hormone

TSAb - thyroid stimulating antibodies

TSH - thyroid-stimulating hormone

WHO - World Health Organization

CONTENTS

OVERVIEW OF THYROID ANATOMY AND FUNCTION

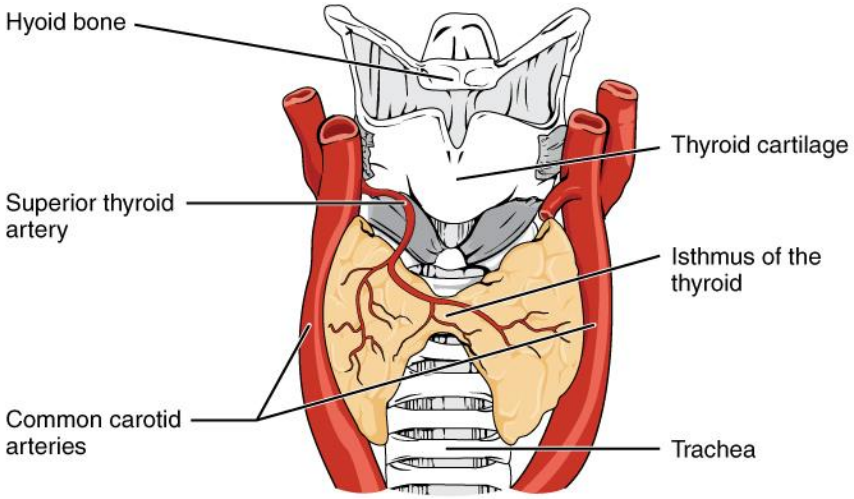
The thyroid gland is located in the anterior neck between the cricoid cartilage and suprasternal notch. It consists of 2 lobes connected by an isthmus. Each lobe of the thyroid gland is embedded with parathyroid glands, which are located on their posterior surfaces. The tissue of the thyroid gland is composed mainly of thyroid follicles (Fig.1). Follicular cells in the gland produce the 2 main thyroid hormones:

- Tetraiodothyronine (thyroxine, T_4)
- Triiodothyronine (T_3)

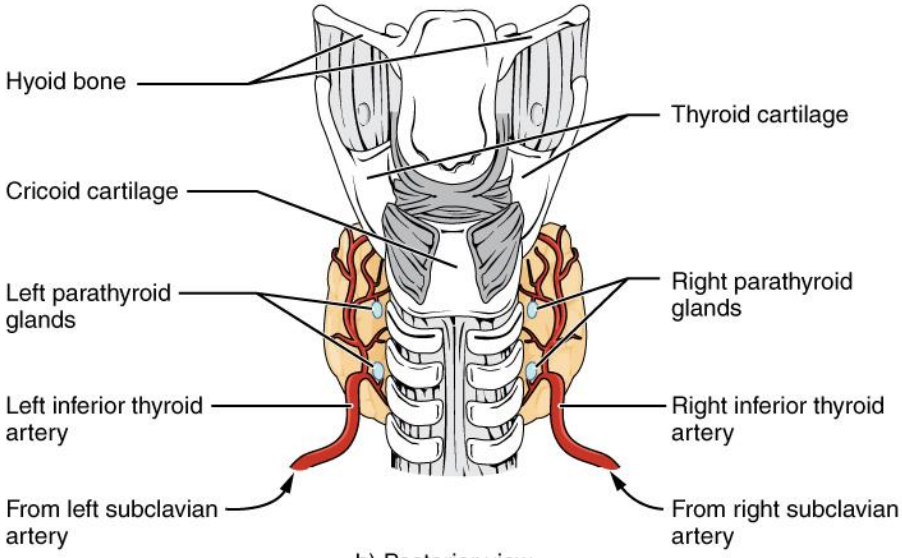
These hormones influence cell functioning in practically every body tissue by connecting with nuclear receptors and shifting expression of a wide range of gene products. Thyroid hormones are required for sufficient brain and somatic tissue development in the fetus and neonate, and they continue to support neurological function in adults. In people of all ages, they regulate protein, carbohydrate, and fat metabolism, heat production, gut peristalsis, influence reproductive function.

T3 is the most active form in combining with the nuclear receptor, while T4 has only minimal hormonal activity. Nevertheless, T4 is much longer lasting and can be converted to T3 in most tissues and therefore serves as a storage for T3. The majority of circulating T3 is produced outside of the thyroid gland by monodeiodination of T4. Only 20% of circulating T3 is secreted directly by the thyroid. In addition, parafollicular cells (C cells) secrete calcitonin, which is the hormone released in response to hypercalcemia and possesses the ability to lower serum calcium levels. Calcitonin plays a minimal role in calcium homeostasis in humans, so the importance of calcitonin is not entirely understood, but the C-cells are important because of their involvement in medullary thyroid cancer.

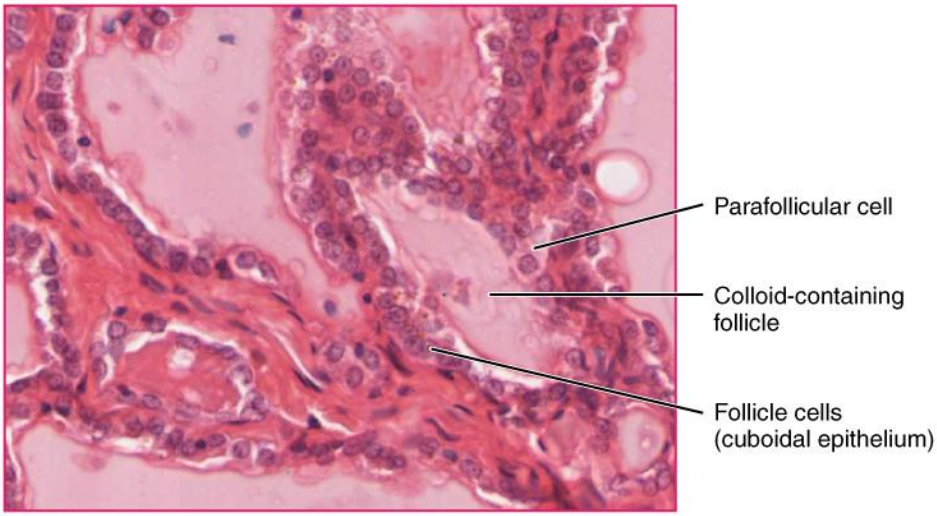
The production of thyroid hormones requires iodine. Iodine is ingested with food and water in the form of iodide. Thyroid gland actively concentrates iodide and converts it to organic iodine by the process of organification, which is going on within follicular cells by thyroid peroxidase.



a) Anterior view



b) Posterior view



c) Thyroid follicle cells

Figure 1. Thyroid Gland. The thyroid gland is located in the anterior neck below the cricoid cartilage. a) Anterior view of the thyroid gland. b) Posterior view of the thyroid gland. c) The tissue is composed primarily of thyroid follicles. Parafollicular cells are larger and often appear within the matrix of follicle cells.

The follicular cells encircle a space filled with colloid, which mainly consists of thyroglobulin (a glycoprotein, which contains tyrosine within its matrix). Tyrosine in contact with the membrane of the follicular cells is iodinated at 1 (monoiodotyrosine) or 2 (diiodotyrosine) sites and then coupled to produce the 2 forms of thyroid hormone (diiodotyrosine + diiodotyrosine = T4; diiodotyrosine + monoiodotyrosine = T3).

T3 and T4 stay incorporated in thyroglobulin within the follicle until the follicular cells adopt thyroglobulin as colloid droplets. Once inside the thyroid follicular cells, T3 and T4 are splitted from thyroglobulin.

Free T3 and T4 are then released into the blood, where they are bound to transport proteins. The main transport protein is thyroxine-binding globulin (TBG), which has high affinity but low capacity for thyroid hormones. TBG normally carries about 75% of bound T3 and T4.

The other binding proteins are thyroxine-binding prealbumin (transthyretin), which has high affinity but low capacity for T4, and albumin, which has low affinity but high capacity for T3 and T4.

About 0.3% of total serum T3 and 0.03% of total serum T4 are free and in balance with bound hormones. Only free thyroid hormones are available to act on the peripheral tissues.

All reactions necessary for the formation and release of T3 and T4 are controlled by thyroid-stimulating hormone (TSH), which is secreted in anterior pituitary by thyrotropic cells. TSH secretion is controlled by a negative feedback mechanism. Increased levels of free T4 and T3 inhibit TSH synthesis and secretion, whereas decreased levels stimulate TSH secretion. TSH secretion is also influenced

by thyrotropin-releasing hormone (TRH), which is synthesized in the hypothalamus (Fig.2). The precise mechanisms regulating TRH synthesis and release are unknown, albeit negative feedback from thyroid hormones inhibits TRH synthesis.

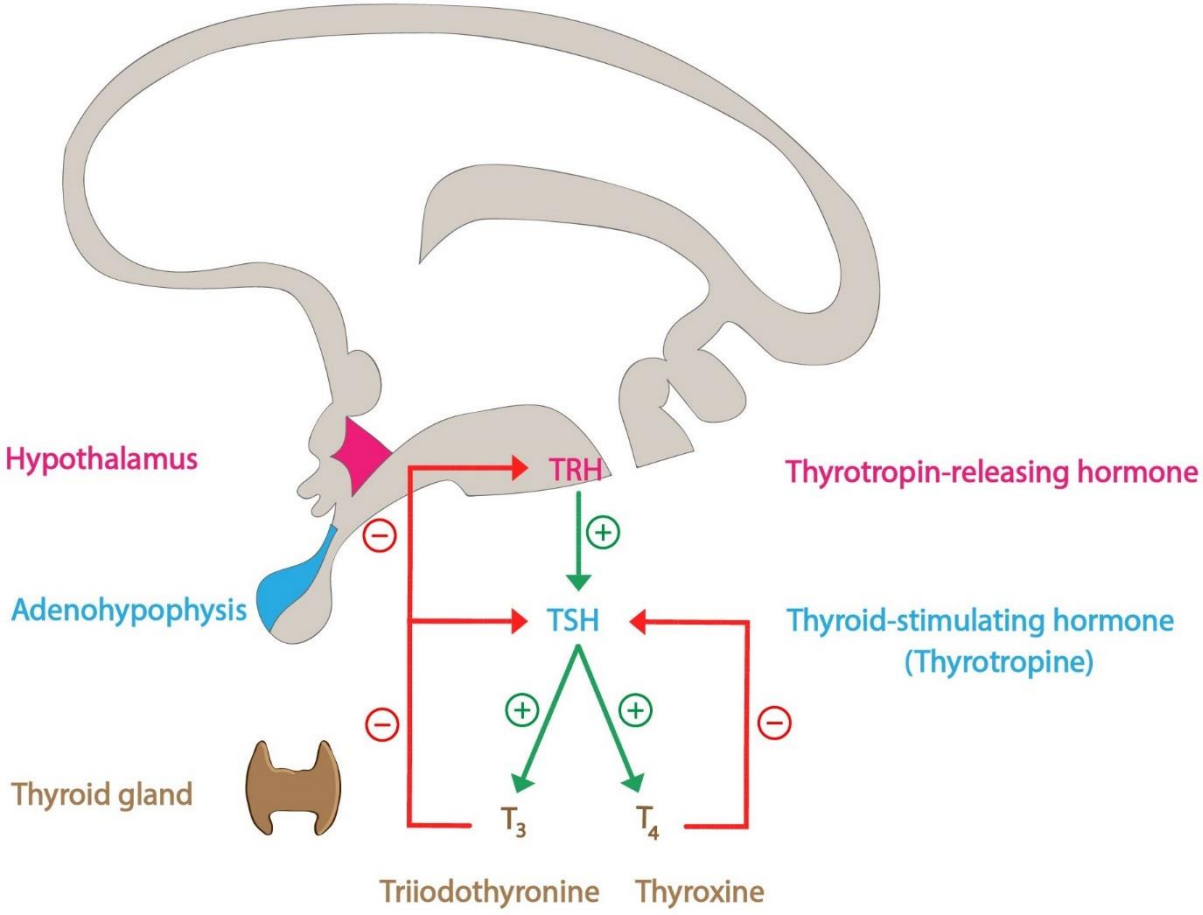


Figure 2. The mechanisms of regulation of thyroid function.

Although TSH is a dominant hormonal regulator of thyroid gland growth and function, a variety of growth factors, most produced locally in the thyroid gland, also influence thyroid hormone production. These include insulin-like growth factor I (IGF-1), epidermal growth factor, transforming growth factor β (TGF-β), endotelins, and various cytokins.

IODINE DEFICIENCY.

Dietary iodine is essential for the synthesis of T_3 and T_4. Most environmental iodine occurs in seawater as iodide; a small amount enters the atmosphere and, through rain, enters ground water and soil near the sea. However, for the large part of the world's population, foods do not provide proper levels of this trace mineral, because the amount varies according to the level in the soil in which the food was grown, as well as the irrigation and fertilizers used. Wild-grown seafood tends to have high levels because it concentrates iodine from seawater, but many people in inland regions lack access to marine fish and other sea products. That's why iodine deficiency is prevalent in many mountainous regions throughout the world and in central Africa, central South America, and northern Asia. Europe remains slightly iodine deficient and statistical data indicate that iodine intake has been decreasing in the United States and Australia. The World Health Organization (WHO) estimates that about 2 billion people in a world suffer from iodine deficiency, the data are based on iodine urinary excretion screening. Thus, the main source of dietary iodine in many countries is iodized salt, bread, vegetable oils. Consuming of iodine-enriched products has markedly reduced the prevalence of cretinism in the world.

Dietary iodine deficiency can result in the abated ability to synthesize T_3 and T_4, leading to a number of severe disorders. When T_3 and T_4 are lacking, TSH is secreted in increasing amounts. As a result of overstimulation by TSH, thyroglobulin is being accumulated in the follicles of thyroid gland, increasing their deposits of colloid. The accumulation of colloid increases the overall size of the thyroid gland. This condition is called a goiter (Figure 3).

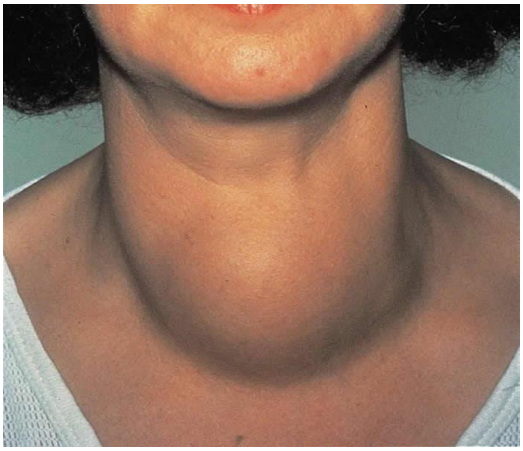


Figure 3.Goiter.

NON-TOXIC GOITER

Non-toxic goiter (diffuse, endemic uninodular or multinodular) is a disease of thyroid gland, characterized by the increase of its size; results from iodine deficiency and is not associated with hyperthyroidism, hypothyroidism, thyroiditis or neoplasm.

Endemic goiter is defined as thyroid enlargement that occurs in more than 10% of a population. A goiter is only a visible sign of the deficiency. If thyroid function is preserved, patients are commonly asymptomatic. The deepening of iodine deficiency or the increase of iodine demand due to puberty, pregnancy, severe somatic diseases may provoke progressive increase of goiter size. Large goiters may cause obstructive symptoms due to compression of the trachea and/or the esophagus. Nodules appear in thyroid gland in 10-15 years of the disease and goiter eventually becomes multinodular. In case of exhaustion of body's compensatory abilities, hypothyrosis might ultimately develop. When iodine deficiency is severe, hypothyroidism and cretinism develop. Cretinism (neonatal hypothyroidism) is characterized by cognitive underdevelopment, short body height, and occasionally deafness and muteness in children and adults born to mothers who were lacking iodine during pregnancy and who weren't treated with iodine or thyroid hormone to restore normal thyroid hormone levels during early childhood. Concomitant selenium, zinc, copper,

manganese deficiency may also contribute to the neurologic manifestations of cretinism.

Other iodine deficiency disorders include stunted growth and development, low fertility, and prenatal and infant death. Moreover, iodine deficiency is the main cause of preventable mental retardation.

Physical examination is aimed to assess thyroid size, consistency, nodularity, and any tenderness or fixation. Examination of the neck begins by inspecting the seated patient from the front and side and noting any surgical scars, obvious masses or distended veins. The thyroid can be palpated with both hands from behind or while facing the patient, using the thumbs to palpate each lobe. The patient's neck should be slightly flexed to relax the neck muscles. After locating the cricoid cartilage, the isthmus can be identified and followed laterally to locate either lobe. Normally, the right lobe is slightly larger than the left. By asking the patient to swallow sips of water thyroid consistence can be better assessed as the gland moves beneath the examiner's fingers. In the early stages, the goiter is typically soft, symmetric, nontender and smooth. Later, multiple nodules and cysts may develop.

Classification of goiter according to the WHO (2008):

Grade 0: No goiter is palpable or visible.

Grade 1: palpable goiter, not visible when neck is held in normal position

Grade 2: a clearly enlarged anterior neck (also visible in normal position of the neck) that is consistent with a goiter on palpation

Diagnosis of non-toxic goiter is based on the presence of goiter, the data of thyroid function test (TFT) and thyroid ultrasound.

TFT includes assessment of TSH, T3 and T4. TSH measurement is the best means of determining thyroid dysfunction. Normal results essentially rule out hyperthyroidism or hypothyroidism. In endemic goiter, serum TSH may be slightly elevated, and serum T4 may be low-normal or slightly low, but serum T3 is usually normal or slightly elevated. As the iodine deficiency progresses and functional ability

of thyroid gland drops, TSH might get increased, levels of T3 and T4 decrease, indicating the beginning of hypothyroidism development.

Thyroid antibodies are measured to rule out Hashimoto thyroiditis.

Thyroid ultrasoundis the method of choice when it is important to determine thyroid size and structure accurately. It allows to detect nodules and cysts ≥2 mm and to monitor their size.Ultrasound-guided fine-needle aspiration (FNA) biopsy of thyroid lesions allows precise assessment of their histological structure and lowers the rate of inadequate sampling.

In the early stages, thyroidal radioactive iodine uptake may be normal or high with normal thyroid scans.

Urinary excretion of iodine allows assessing the level of iodine deficiency in the population. The urinary excretion of iodine is determined in 50-100 people who live at certain territory. Normal iodineuria in teenagers and adults is 100 mcg/L and above.

Treatment and prevention

All patients who were diagnosed with hypothyroidism should be prescribedwith L-thyroxine in the doses necessary to achieve euthyroidism. It is prescribed to patients with 2^{nd} degree goiter to reduce the TSH content in the blood. The dose of L-thyroxine ranges from 100 to 150 micrograms per day. This requires careful monitoring of the patient's condition. The appearance of sweating, palpitations, irritability may indicate an overdose of L-thyroxine or the presence of autonomous nodes.

Patients with large goiters are treated surgically, when the function of several adjacent organs is deranged. Goiters with signs of malignancy also require surgical treatment.

The elimination of iodine deficiency is achieved by iodine prevention: mass, group, individual.

Mass prevention is performed to everyone living at iodine deficient territories. The use of iodized salt is an effective method. Iodization is done with potassium iodide and potassium iodate. The oil solution of iodine can be also used for mass prevention. It provides the body with iodine for 6-12 months when taken orally, 1-3 years – when given in intramuscular injection.Iodine preparations (potassium iodide, 200 mcg 1/day) are used for individual and group prevention.

Group prevention is an additional provision of iodides against the background of mass prevention for those categories of persons, who have increased need for iodine: pregnant and lactating women, children, teenagers.

The recommended average daily intake of iodine for adults is 150-250 mcg/d, for children – 90-120 mcg/d, for pregnant and lactating women – 250 mcg/d. The oversupply of iodine is associated with an increased incidence of autoimmune thyroid disease.

Individual prevention is performed for individuals with an increased personal need for iodine. These include women a year before the planned pregnancy; patients recovering from severe somatic or infectious diseases;patients finishing courses of antibiotic therapy or treatment with sulfonamides; people with lesions of the digestive system, when iodine absorption is affected.

SPORADIC NONTOXIC GOITER

Sporadic nontoxic goiter (SNG) is defined as a benign enlargement of the thyroid gland in a euthyroid person, who lives in an iodine-sufficient area. This type of goiter is 10 times more common in women than in men and it occurs around puberty in both genders and during pregnancy and lactation in women suggesting its relation to the physiological demand for iodine. The incidence decreases with age in both genders, and there is significant geographic variation in nonendemic goiter areas for the development of sporadic simple goiter. The cause of SNG is thought to be relative iodine deficiency. In addition, other factors that play a significant role include presence of dietary goiterogens (cassava, maize, bamboo shoots, sweet potatoes, lima

beans, broccoli, cabbage), certain chemicals that interfere with thyroid hormone synthesis, and certain drugs, such as paramino-salicylic acid, sulphonylureas, lithium,and excessive iodine. Also autoimmune and genetic factors play a role. A large number of patients demonstrate no obvious cause of SNG.

SNG can be diffuse, uninodular, or multinodular and can vary greatly in size, growth rate, and clinical presentation. SNG is a common essence in clinical practice, because patients often present with a small, diffuse goiter or a solitary palpable nodule.

The natural history of SNG is characterized by gradual increase of size, with eventual development of multiple nodules, possible appearance of local compressive symptoms, and/or cosmetic issues. The growth rate is changeable, and patients may have stable goiter size for many years.

With the passage of time, there is a tendency for SNGs to form nodules, which can become autonomous and eventually cause subclinical or overt hyperthyroidism. It is found that hyperthyroidism develops in approximately 10% of patients with SNG after 10 years of monitoring, however most of those patients had suppressed TSH levels and subclinical hyperthyroidism on presentation.

The lab investigation of a patient with a SNG should begin with a determination of TSH level in blood, because many patients who are clinically euthyroid have biochemical evidence of hypo- or hyperthyroidism. The degree of thyroid malfunction is often mild or subclinical, proven by an isolated TSH abnormality. Both subclinical and overt hypothyroidism should be treated, to reverse or prevent symptoms as well as prevent further gland enlargement. Apparent hyperthyroidism should also be treated, especially because many patients with SNG and hyperthyroidism are elderlies and have increased cardiac risks. It is more problematic to decide whether to treat subclinical hyperthyroidism, which is the most common thyroid function disorder in SNG. An increasing number of evidence suggests that subclinical hyperthyroidism is

harmful to the heart, bone, and cognitive function. Therefore treatment decisions should take into account these risks in an individual patient.

Ultrasound should be done all patients, because approximately 50% have multiple nodules that are not detected on physical examination. Also, periodical ultrasound measurements are very sensitive in detecting nodule growth. Upon discovery of nonpalpable nodules, a fine-needle aspiration biopsy should be done to any nodule that is 1–1.5 cm in diameter and above, to exclude the presence of thyroid cancer, as recommended by international endocrinology societies. The sonographic signs suggestive of nodule malignancy are the following: the presence of microcalcifications, hypoechogenicity, increased vascularity, rapid growth, uneven borders.

Radioiodine uptake. The thyroid gland selectively transports radioisotopes of ^{123}I, ^{125}I, ^{131}I, allowing thyroid imaging and quantitation of radioactive tracer uptake, so the visualization of nodules and determination of their function can be done.

The treatment goals for a patient with a benign SNG include relief of local compressive symptoms or cosmetic deformity, prevention of progressive thyroid growth, and treatment of corresponding thyroid dysfunction. These symptoms vary greatly among patients, from those with no symptoms and an accidentally discovered goiter to those with compression of adjacent organs. Therefore, there is no optimal treatment for SNG, and treatment decisions must be personalized.

As for SNG, four main treatment options exist:

- follow-up without treatment;
- thyroidectomy;
- levothyroxine (L-thyroxine) suppression;
- radioactive iodine.

Follow-up without treatment. A period of cautious waiting in patients with no local symptoms or thyroid dysfunction is often the best option. Such patients should

be properly monitored by clinical examination and repeated ultrasound measurements of overall thyroid and nodule size should be done.

Thyroidectomy is an appropriate option in SNG. Many factors should be considered when making a pro-surgery decision, including patient's general health condition, size of goiter, symptomatology, and availability of skilled surgeon.

Indications to surgical treatment of nodular goiter:

- Nodes with signs of malignancy
- Autonomic adenomas
- Retrosternal nodes
- Nodes that rapidly increase in size, regardless of their cellular composition
- Nodes, squeezing the organs of the neck and mediastinum.
- Nodes in children, women up to 20 years of age, men of all ages.

The long-term recurrence rate after surgical treatment depends on the extent of operation, ranging from 0% for total thyroidectomy to 60% for unilateral thyroidectomy. The average time to recurrence can take many years, and most patients with recurrence do not need reoperation. Postoperative treatment with L-thyroxine does not affect the recurrence rates.

L-thyroxine suppression. L-thyroxine is used in doses meant to suppress TSH. As we know, TSH is a growth factor for SNG and suppressing TSH levels removes this growth stimulus and causes goiter stabilization. However, several placebo-controlled studies have been disappointing concerning goiter shrinkage, although one study registered a prevention of nodule growth with L-thyroxine over 5 year period.

SNGs typically regrow when L-thyroxine is discontinued, necessitating uncertain treatment. In this case patient may have subclinical hyperthyroidism for many years. Contemporary knowledge suggests that subclinical hyperthyroidism causes bone loss, increased risk of atrial fibrillation and other heart disorders. Also, neuropsychiatric and cognitive effects can be seen. The equivocal long-term efficacy of TSH

suppression, combined with these risks, has led to a descent of enthusiasm concerning this treatment option.

Radioactive iodine. The first reports of the use of radioactive iodine for the treatment of large multinodular goiters appeared in the 1960s, and a series of uncontrolled studies followed. The size of the goiter decreased in all cases by 40% or more, and most patients had significant relief of compressive symptoms. Iodine-131 (^{131}I) was used for treatment. Side effects were mild, except the high rates of hypothyroidism development. Another possible side effect includes the risk of radioiodine-induced carcinogenesis: a slight increase in rates of kidney, stomach, bladder, breast, and brain cancers were documented. The problem is that ^{131}I doses for SNG are typically higher than those proposed for treatment of Graves' disease, and, therefore, the extrathyroidal tissue exposure is much higher than that obtained when treating Graves' disease. Therefore, this might be a problem, especially for young patients, and has to be discussed with them in the realms of whether to choose surgery or radioactive iodine therapy for SNG.

If the administered dose of ^{131}I is a problem, then efforts to improve treatment effectiveness of SNG while minimizing ^{131}I doses make sense. A reasonable option is the use of recombinant human TSH (rhTSH) in SNGs. rhTSH promotes iodine uptake into both normal and abnormal thyroid tissue. Very low doses of rhTSH (0.01 and 0.03 mg) significantly increase 24-h radioactive iodine uptake in patients with multinodular goiters. This method is very promising and allows to minimize side effects of radioiodine therapy in patients with SNG.

Review questions:

1. Which of the following statements about the thyroid gland is true?
   A. It is located anterior to the trachea and inferior to the larynx.
   B. The parathyroid glands are embedded within it.
   C. It produces three hormones.
   D. All of the above
2. The secretion of thyroid hormones is controlled by:
   A. TSH from the hypothalamus
   B. TSH from the anterior pituitary
   C. Thyroxine from the anterior pituitary
   D. Thyroglobulin from the thyroid's parafollicular cells
3. The development of a goiter indicates that:
   A. The anterior pituitary is abnormally enlarged
   B. There is hypertrophy of the thyroid's follicle cells
   C. There is an excessive accumulation of colloid in the thyroid follicles
   D. The anterior pituitary is secreting excessive growth hormone
4. Iodide ions cross from the bloodstream into follicle cells via:
   A. Simple diffusion
   B. Facilitated diffusion
   C. Active transport
   D. Osmosis
5. Which assay allows differentiating between endemic goiter and sporadic goiter?
   A. Serum TSH
   B. Ultrasound of the thyroid gland
   C. Radioiodine uptake by the thyroid gland
   D. Urinary excretion of iodine
6. The chronic oversupply of iodine is associated with an increased incidence of:
   A. Autoimmune thyroid disease

B. Hypothyroidism

C. Thyrotoxicosis

D. Thyroid cancer

7. The types of iodine deficiency prevention in endemic region include:

A. Mass prevention

B. Group prevention

C. Individual prevention

D. All of the above

8. The treatment of endemic non-toxic diffuse goiter as a rule should be:

A. Surgical

B. Conservative

C. Radioiodine

D. Combined

9. What is the purpose of a radioiodine uptake study?

A. Determination of the size of the thyroid gland

B. Determination of the functional state of the thyroid gland

C. To detect the presence of nodes and determine their functional state

D. Determination of structure of the thyroid gland

10. What dosage of L-thyroxine should be prescribed to patients with 2^{nd} degree goiter and above who have an increased TSH content in the blood?

A. 1 mcg/kg

B. 2 mcg/kg

C. 0.5 mcg/kg

D. 3 mcg/kg

HYPOTHYROIDISM

Hypothyroidism is a syndrome, characterized by thyroid hormone deficiency.

Etiological classification of hypothyroidism:

- Primary: caused by disease in the thyroid
- Secondary: caused by disease in the hypothalamus or pituitary

Primary hypothyroidism develops because of the disease in the thyroid gland itself. TSH in this case is increased. The most common cause is autoimmune lesion. It usually occurs due to Hashimoto thyroiditis and the goiter is firm on palpation. As disease progresses, a shrunken fibrotic thyroid can be palpated with little or no function. The second most common cause is iatrogenic hypothyroidism, which is typically caused by radioactive iodine therapy or thyroidectomy for hyperthyroidism or goiter. Overtreatment with antithyroid medications like propylthiouracil, methimazole, and iodide might cause hypothyroidism, however, it abates after therapy is stopped.

Endemic goiter can be the reason for goitrous hypothyroidism due to iodine deficiency. Iodine deficiency lowers the production of thyroid hormones. As the result, TSH is released, which stimulates thyroid gland to grow and trap iodine actively, therefore, goiter develops. Patient with endemic goiter becomes hypothyroid if iodine deficiency is severe and prolonged.

Goitrous hypothyroidism can be also caused by rare inherited enzymatic defects can modify the synthesis of thyroid hormone. Congenital goiters may be caused by dyshormonogenesis (abnormal thyroid hormone production), transplacental passage of maternal antibodies, or transplacental passage of goitrogens. Some causes of congenital goiter are hereditary. Also, aplasia and hypoplasia of thyroid gland can be the cause of hypothyroidism.

Infiltrative disorders that might cause primary hypothyroidism are the following: amyloidosis, sarcoidosis, hemochromatosis, scleroderma.

Administration of lithium can be potential reason for hypothyroidism, because lithium inhibits hormone release by the thyroid.

Some medications like amiodarone or other iodine-containing drugs; interferon-alfa; checkpoint inhibitors or tyrosine kinase inhibitors for cancer can also induce hypothyroidism. Hypothyroidism may result from radiation therapy for laryngeal cancer or Hodgkin's lymphoma.

Secondary (central) hypothyroidism occurs when the hypothalamus does not produce enough TRH or the pituitary gland does not produce enough TSH. Sometimes insufficient secretion of TSH due to insufficient secretion of TSH is called tertiary hypothyroidism. The causes for central hypothyroidism are the following: pituitary adenomas, previous pituitary/hypothalamic surgery or radiotherapy, history of head trauma, history of pituitary apoplexy, hypothalamic/suprasellar tumors.

Subclinical hypothyroidism is characterized by increased serum TSH in patients with minimal or no symptoms of hypothyroidism and normal serum levels of free T4.

Subclinical hypothyroidism is relatively common. It occurs in more than 15% of elderly women and 10% of elderly men, especially in those with underlying Hashimoto thyroiditis.

Patients, whose plasma TSH is above 10 mU/L, have high probability of progression to overt hypothyroidism with low plasma levels of free T4 in the next 10 years. Such patients are also more prone to hypercholesterolemia and atherosclerosis. They should be prescribed L-thyroxine, even if they are asymptomatic.

A trial of L-thyroxine makes sense for patients with TSH levels between 4.5 and 10 mU/L if symptoms of early hypothyroidism (for example fatigue, forgetfulness, depression) are present.

A therapy with L-thyroxine is also indicated for pregnant women and those women who plan to become pregnant in order to avoid the harmful effects of hypothyroidism on the course of pregnancy and fetal development. Patients should have their TSH and free T4 measured annually to evaluate the dynamics of condition if untreated, or to adjust the dosage of L-thyroxine.

Peripheral hypothyroidism is a type of permanent congenital hypothyroidism that results from peripheral defects in thyroid hormone metabolism. Peripheral hypothyroidism may be caused by peripheral resistance to the action of thyroid hormone due to dominantly inherited mutations in genes encoding for thyroid hormone receptor beta. The majority of these individuals have normal thyroid function. Peripheral hypothyroidism may also be caused by defects in thyroid hormone transport, such as in Allan-Herndon-Dudley syndrome where X-linked peripheral hypothyroidism is associated with mental retardation and neurologic abnormalities including quadriplegia.

Transient hypothyroidism develops in case of certain diseases of thyroid gland or might result from some treatment strategies of thyroid diseases. It is prone to spontaneous disappearance after elimination of etiologic factors. It may occur in patients with silent thyroiditis, including postpartum thyroiditis, subacute thyroiditis, withdrawal of thyroxine treatment in patients with intact thyroid, after ^{131}I treatment or subtotal thyroidectomy for Grave's disease.

Pathogenesis: the pathogenetic basis of clinical hypothyroidism is derangement of all types of metabolism as a result of thyroid hormones deficiency, which results in decline of basic metabolic rates. These changes are especially manifested in the organs and tissues that are intensively renewed. Erythropoiesis slows down and anemia develops. Due to the slowing down of lipid metabolism, free fatty acids, triglycerides, and cholesterol accumulate in the body. The particular role is played by the disorders of protein metabolism. As the result of slowing down of protein metabolism, the accumulation of proteinaceous ground substance is going

on, which includes derivatives of proteins, as well as glucuronic and chondroitinic acids. Proteinaceous ground substance accumulates in interstitia, causing mucinous edema. Due to the high hydrophilicity of proteinaceous ground substance there is accumulation of significant amount of sodium, chlorides and waterin the extra-vascular structures (eg., skin, heart, muscles, body cavities). This leads to the development of hydrothorax, hydropericardium, and ascites. In children, the deficiency of thyroid hormones causes a slowing of growth, physical, mental, sexual development, up to the growth retardation and cretinism. In the primary hypothyroidism there is an absence of inhibitory effects towards the release of thyrotropin and thyroliberin, so the latter is produced affluently. Due to the immunological and structural proximity of thyroliberin and prolactoliberin, a secretion of prolactin is promoted and galactorrhea develops.

Signs and symptoms:

- Metabolic manifestations: Cold intolerance, moderate weight gain (due to fluid retention and slowed metabolism), hypothermia;
- Neurologic manifestations: Forgetfulness, impaired concentration, paresthesias of the hands and feet (develop due to carpal tunnel syndrome caused by deposition of proteinaceous ground substance in the ligaments around the wrist and ankle); retardation of the relaxation phase of deep tendon reflexes;
- Psychiatric manifestations: Dull facial expression, personality changes, depression, dementia or frank psychosis (myxedema madness);
- Dermatologic manifestations: Sparse, coarse and dry hair; facial puffiness; myxedema; loss of lateral eyebrows, coarse, dry, scaly and thick skin; macroglossia due to deposition of proteinaceous ground substance in the tongue; carotenemia, particularly notable on the palms and soles (caused by deposition of carotene in the lipid-rich epidermal layers);

- Ocular manifestations: Dropping eyelids because of decreased adrenergic drive; periorbital swelling due to infiltration with the mucopolysaccharides, hyaluronic acid and chondroitin sulfate);
- Gastrointestinal manifestations: Constipation;
- Gynecologic manifestations: Menorrhagia or secondary amenorrhea, reduced fertility, miscarriages;
- Cardiovascular manifestations: Bradycardia (a decrease in both thyroid hormone and adrenergic stimulation causes slow heart rate), enlarged heart on examination and imaging (mainly because of pericardial effusion, but dilation also contributes), hypertension (primarily diastolic);
- Other manifestations: Hoarse voice, and slow speech; pleural and/or abdominal effusions (pleural effusions develop slowly and only rarely cause respiratory or hemodynamic distress).

The appearance of symptoms depends on the degree of hypothyroidism severity.

Although secondary hypothyroidism is very rare, its etiological causes often affect other endocrine organs controlled by the hypothalamic-pituitary system. Secondary hypothyroidism is characterized by the fact that the skin and hair are dry, but not very rough, there is skin depigmentation, minimal macroglossia, atrophic breasts and low blood pressure. In addition, the heart is small, and serous pericardial effusions do not occur. Hypoglycemia is common due to concomitant adrenal insufficiency or growth hormone deficiency.

Myxedema coma is a life-threatening complication of hypothyroidism. It usually occurs in older patients with a long history of hypothyroidism. Myxedema coma almost always occurs in the elderly. Precipitating factors include infection, illness, drugs that suppress the CNS (particularly sedatives, anesthetics, antidepressants), trauma, and exposure to cold. There may be a history of treated hypothyroidism with poor compliance, or the patient may be previously

undiagnosed. Hypoventilation, leading to hypoxia and hypercapnia, plays a major role in pathogenesis; hypoglycemia and dilutional hyponatremia also contribute to the development of myxedema coma. The coma is characterized by extreme hypothermia (body temperature 24° to 32.2° C), seizures, areflexia, and inhibition of respiratory functions with carbon dioxide retention. Assessment of severe hypothermia requires usage of low-reading thermometers, otherwise it can be missed. Prompt diagnosis based on history, physical examination and express lab data is vitally important, because death is likely without quick treatment.

Diagnosis. The diagnosis of hypothyroidism is made from the history, the clinical picture and the laboratory measurements.

TSH and free T4 measurement are the laboratory examinations necessary for the diagnosis of hypothyroidism and the differential diagnosis between primary (clinical or subclinical) and secondary one.

When TSH is increased and free T4 is decreased or normal hypothyroidism is primary. In this case increased anti-TPO or anti-Tg antibodies point to the cause of hypothyroidism, which is autoimmune thyroiditis. Primary hypothyroidism is divided in clinical when TSH is increased and free T4 is decreased and in subclinical when TSH is increased and free T4 is normal.

Many patients with primary hypothyroidism have normal circulating levels of triiodothyronine (T3), which is probably due to prolonged TSH stimulation of the failing thyroid gland, which leads to the predominant synthesis and secretion of biologically active T3. Therefore, serum T3 is not sensitive for hypothyroidism.

When TSH is normal or decreased and free T4 is low hypothyroidism is secondary (central). In order to discriminate whether the cause is in the pituitary or the hypothalamus a test with the TSH releasing factor is performed (TRH test). In the first case the response is normal, while in the second it is abnormal. In central hypothyroidism imaging studies of the brain and the pituitary (MRI, CT) are performed aiming at finding its cause.

Usually the reported normal limits of TSH are between 0.4-4.0 mU/l. When TSH is found in the upper normal limits it may show mild hypothyroidism which may progress to hypothyroidism, especially if antibodies are increased.

TSH may be increased in euthyroid individuals in certain situations. Increased TSH (5-20 mU/l) is observed during convalescence from non-thyroidal illness (euthyroid sick syndrome), as well in pituitary adenomas producing TSH or in isolated resistance of the pituitary to thyroid hormones. Finally, TSH increase may be observed in chronic renal failure and in primary adrenal insufficiency.

Complete blood count may demonstrate the presence of anemia, usually normocytic-normochromic. In some cases, anemia may be hypochromic because of menorrhagia and sometimes macrocytic because of associated vitamin B_{12} or B_9 deficiency. Anemia is rarely severe and Hb level is usually > 90 g/L. Anemia usually subsides as the hypometabolic state is corrected, which sometimes takes 6 to 9 months.

Serum cholesterol and triglycerides are usually elevated in primary hypothyroidism but not so much in secondary hypothyroidism.

Hypothyroidism is associated with atherosclerosis, endothelial dysfunction, increased carotid intima-media thickness and impaired cardiac contractility.

Treatment

Various thyroid hormone preparations can be used for replacement therapy, the most common are: synthetic preparations of T4 (l-thyroxine), T3 (liothyronine), combinations of two synthetic hormones, and desiccated animal thyroid extract. L-Thyroxine is a drug of choice, the usual maintenance dose is 75 to 150 mcg per os once a day, depending on age, body mass index, and the intensity of absorption. The beginning dose in young patients or those of middle age, who are otherwise healthy, can be 100 mcg or 1.7 mcg/kg per os once a day.

A careful approach should be applied to patients with heart disease, the therapy should begin with low doses for them, which is usually 25 mcg once a day. The dose

is higher in individuals having been subjected to thyroidectomy than those with chronic autoimmune thyroiditis, as in those there are remnants of functioning thyroid tissue. In subclinical hypothyroidism the dose is low (0.5 μg/kg). In pregnancy, a larger dose is required (2 μg/kg). During pregnancy the increase in dose that may be required is 25-47% more than the one before pregnancy and it is observed during the 4^{th} to 6^{th} week. In all cases the dose should be adjusted every 6 weeks until maintenance dose is reached. An increase of dose may be needed if drugs that decrease T4 absorption or increase its biliary excretion are administered concomitantly. The dose used should be the lowest that provides achievement of the midnormal range of serum TSH or its lower normal limits (approximately 1.0 mU/l). TSH measurement after the initiation of therapy is performed every 4-6 weeks. The follow-up is performed by TSH measurement once every year. In pregnancy the first TSH measurement should be performed when pregnancy is diagnosed and thereafter every 3-4 weeks during the first half of the pregnancy and every 6 weeks thereafter. The evaluation of TSH cannot be used to control the efficacy of treatment in patients with secondary hypothyroidism. In secondary hypothyroidism the dose of L-thyroxine should achieve a free T4 in the midnormal range.

The clinical effects of treatment with l-thyroxine appear slowly. Patients may not have full relief from symptoms until 3-6 months after midnormal TSH levels are restored.

Great caution is needed in substitution therapy with thyroxine as dose overestimation has consequences. It has been observed that more than one fifth of the patients have clinical or subclinical hyperthyroidism. These consequences are atrial fibrillation, aggravation of coronary artery disease and a decrease in bone mineral density, fractures of the spine and the hip being observed in women >65 years.

Liothyronine (L-triiodothyronine) has short half-life and produces the large peaks in serum T3 levels, therefore it shouldn’t be used alone for long-term

replacement therapy. The use of standard replacement amounts (from 25 to 37.5 mcg twice a day) leads to a rapid increase in serum T3 levels to 300-1000 ng/dl (4.62-15.4 nmol/L) within 4 hours because of its almost complete absorption. These levels return to normal by 24 hours. In addition, patients receiving liothyronine develop chemical hyperthyroid state for at least several hours a day, which potentially increases the risk of heart disease.

Similar fluctuations of serum T3 occur when mixed preparations of T3 and T4 are taken per os. Although the peak of T3 in this case is lower because less T3 is given.

Replacement therapy with L-thyroxine produces different pattern of serum T3 response. Serum T3 levels increase gradually, and normal levels are maintained when adequate doses of T4 are given. The use of desiccated animal thyroid extracts demonstrates less controllable clinical effect because they contain different amounts of T3 and T4, and should not be prescribed unless the patient is already taking the preparation and has normal serum TSH.

In patients with secondary hypothyroidism, the administration of l-thyroxine can potentially precipitate adrenal crisis, therefore l-thyroxine should not be given until there is an evidence of adequate cortisol secretion, or cortisol therapy is given concomitantly.

Treatment of myxedema coma. In myxedema coma, the danger of death was 60-70% in 1985 but it has decreased to 20-25%, owing to the timely diagnosis and the referral of patients to acute care units.

Levothyroxine can initially be administered as a single IV bolus of 500 mcg, which serves as a loading dose. Although further levothyroxine is not strictly necessary for several days, it is usually continued at a dose of 50-100 mcg/day. If suitable IV preparation is not available, the same initial dose of levothyroxine can be given by nasogastric tube (however, absorption can be altered in myxedema). An alternative is to give liothyronine (T3) IV or via nasogastric tube in doses 10-25 mcg

every 8-12 hours. This treatment has been advocated because T4 to T3 conversion is impaired in myxedema coma. The problem is that excess liothyronine can provoke arrhythmias. An acceptable option is to combine levothyroxine (200 mcg) and liothyronine (25 mcg) as a single, initial IV bolus, followed by daily treatment with levothyroxine (50-100 mcg) and liothyronine (10 mcg every 8 hours).

Supportive therapy should be provided to correct any associated metabolic disturbances. External warming is indicated only if the body temperature is below 30 degrees Celsius, as it can precipitate hypotension or arrhythmias. Otherwise patient should be covered with blanket to conserve heat. Parenteral hydrocortisone (50 mg every 6 hours) should be administered, because there is impaired adrenal reserve in profound myxedema. The precipitating factors should be rapidly and appropriately treated, including the early use of broad spectrum antibiotics, pending the exclusion of infection. Hypoxemia is a common condition, so partial pressure of oxygen should be monitored. If ventilation is jeopardized, immediate mechanical ventilatory assistance is needed. Hypertonic saline or IV glucose may be needed if there is severe hyponatremia or hypoglycemia. The fact that metabolism of most medications is slowed down should be noted. Sedatives should be avoided if possible or used in low doses.

Hypothyroidism and insulin resistance.

Several studies have shown overt and subclinical hypothyroidism being more prevalent in patients with diabetes mellitus than in general population, and women with subclinical hypothyroidism are believed to be at more risk to develop gestational diabetes. The thyroid hormones are known to have a stimulating effect on maturation of the insulin secreting beta cells, and thyroid hormone receptors have been detected in these cells. Thyroid hormones enhance gluconeogenesis and glycogenolysis in an opposing effect to insulin, whereas, they are known to facilitate the cellular glucose uptake by expressing the glucose transporter-4 (GLUT-4) isozyme.

Clinical hypothyroidism is considered to be a risk factor for insulin resistance. Patients with hypothyroidism are characterized by slowing of intestinal glucose absorption and a decrease in the adrenergic activity, leading together to a reduction in liver and muscle glycogenolysis, as well as a decrease in gluconeogenesis and baseline insulin secretion. At the same time, a postprandial increase in insulin secretion against the background of generalized peripheral insulin resistance has been observed, associated with a higher concentration of free fatty acids, reduced glucose uptake and increased glucose oxidation. Thus, hypothyroidism causes a drop in insulin-dependent glucose utilization.

A strong influence of TSH on the fasting insulin levels and the insulin resistance was revealed. Some studies have indicated the effect of TSH on insulin action and that even a subtle increase in plasma TSH levels within the normal range can affect insulin secretion and may cause insulin resistance and metabolic syndrome. Moreover, hypothyroid patients are known to experience a decrease in glucose transporters GLUT4 leading to a reduction of glucose uptake and promoting insulin resistance. The relationship between thyroid hormonal status and insulin levels in the pathogenesis of insulin resistance is complex. The higher fasting serum insulin concentrations were believed to develop as a compensation result of the insulin resistance. Many authors accept the concept that a patient suffering from an autoimmune disorder is more prone to be affected by an autoimmune disorder of insulin resistance. Other investigators relate the occurrence of insulin resistance among hypothyroid patients to the high prevalence of obesity and the high fat deposits in this population.

Also, a reduced ability of insulin to increase blood flow in tissues in hypothyroidism was observed. This may be an alternative mechanism explaining the effect of hypothyroidism on decreasing glucose utilization by peripheral cells.

Review questions:

1. One of the symptoms of hypothyroidism is:
   A. Fatigue
   B. Intolerance to cold
   C. Hair loss
   D. All of the above
2. Although the symptoms of hypothyroidism may be difficult to detect, if hypothyroidism is suspected, the condition can best be diagnosed with:
   A. MRI scan
   B. Ultrasound
   C. Thyroid stimulating hormone test (TSH)
   D. Hemoglobin test or hematocrit test
3. In women, hypothyroidism can affect pregnancy by:
   A. Reducing the chance of getting pregnant
   B. Boosting the chance of getting pregnant
   C. Making miscarriage more likely
   D. Making labor and delivery more difficult
4. A person with untreated hypothyroidism may also suffer from:
   A. High cholesterol
   B. Low blood pressure
   C. Low blood sugar
   D. None of the above
5. How is hypothyroidism treated?
   A. With radiation
   B. With surgery
   C. With a synthetic hormone
   D. The condition can't be treated
6. What disease causes the most significant deceleration of Achilles tendon reflex?

A. Diabetes mellitus

B. Atherosclerosis

C. Hypokalemia

D. Primary hypothyroidism

7. What assay helps to perform the differential diagnosis between primary and secondary hypothyroidism?

A. Determination of T3 and T4 level in blood

B. Determination of TSH in blood

C. Determination of thyrotropin-releasing hormone

D. Determination of prolactin

8. What assay helps to perform the differential diagnosis between secondary and tertiary hypothyroidism?

A. Determination of TSH in blood

B. Determination of thyrotropin-releasing hormone

C. Determination of prolactin

D. Determination of T3 and T4 level in blood

9. The main reason for galactorrhea in patients with hypothyrosis is:

A. Deficiency of thyroid hormones

B. ExcessiveTSH

C. Hypersecretion of thyroliberine

D. All of the above

10. The major role in the pathogenesis of myxedema coma belongs to:

A. Hypoventilation, leading to hypoxia and hypercapnia

B. Progressive decline in cardiac output

C. Hypothermia and increasing hypocorticism

D. Hypoglycemia and dilutional hyponatremia

THYROIDITIS

Thyroiditis is a general term that refers to the presence of inflammatory process in the thyroid gland. Thyroiditis includes a group of individual disorders causing thyroidal inflammation but presenting in different ways.

Classification:

1. Acute thyroiditis (diffuse or local):
   a) suppurative;
   b) nonsuppurative.
2. Subacute thyroiditis:
   a) diffuse;
   b) local.
3. Chronic thyroiditis:
   a) autoimmune thyroiditis (Hashimoto's thyroiditis);
   b) invasive fibrous (Riedel's thyroiditis);
   c) specific thyroiditis (tuberculosis, lues);
   d) caused by physical or chemical agents;
   e) parasitic.

Acute thyroiditis

Acute thyroiditis is rare and usually develops due to suppurative infection (especially Staphylococcus, Streptococcus and Enterobacter) of the thyroid. The most common cause in young patients is the presence of a piriform sinus, which is a remainder of the fourth branchial pouch that connects the oropharynx with the thyroid. A piriform sinus is usually left-sided. Acute thyroiditis can also develop in the elderly and the risk factors are the long-existing goiter and degeneration in thyroid malignancy.

Clinical presentation includes thyroid pain, which radiates to throat or ears, and a small, tender goiter that may be asymmetric. Febrile fever and lymphadenopathy are common, as well as the changes over the thyroid location: erythema, fever, dysphagia.

Lab data: complete blood count (CBC) - elevation of white cell count and erythrocyte sedimentation rate (ESR). TFT – normal T3, T4, and TSH.

FNA biopsy shows infiltration by polymorphonuclear leukocytes; culture of the sample and Gram stain can identify the microorganism.

Immunocompromised patients should be treated with a special attention as fungal (Aspergillus, Candida, Histoplasma), mycobacterial, or Pneumocystis carinii thyroiditis can occur in these cases.

Treatment: prompt administration of antibiotic therapy. Surgery might also be needed to drain the abscess, which can be localized either by ultrasound or by CT scan.

Complications: tracheal obstruction, septicemia, retropharyngeal abscess, mediastinitis, jugular venous thrombosis. Complications may be successfully avoided with prompt use of antibiotics.

Acute thyroiditis can be also non-suppurative. It can result from radiation injury after ^{131}I treatment or usage of amiodarone.

Subacute thyroiditis

(de Quervain Thyroiditis; Giant Cell Thyroiditis; Granulomatous Thyroiditis)

Subacute thyroiditis is an inflammatory disease of the thyroid probably caused by a virus. History of an antecedent viral infection of upper respiratory tract is common. Viruses like mumps, coxsackie, influenza, adenoviruses may play a role. However, the identification of a virus in an individual patient doesn't influence the treatment. The peak incidence occurs at 30-50 years; women get sick 3 times more often than men.

There is inflammation with characteristic giant cell infiltration, polymorphonuclear lymphocytes, and follicular disruption. The follicular changes progress to granulomas, accompanied by fibrosis. In several months thyroid gland returns to normal.

Phases of the disease:

1. Hyperthyroid (3-4 weeks). Follicular destruction causes release of Tg and thyroid hormones, leading to increase of circulating T3 and T4 and suppression of TSH. At this phase, radioactive iodine uptake is low or undetectable (Fig.4).
2. Hypothyroid (6-8 weeks). Thyroid gland is depleted of stored hormones, there is low T3 and T4. TSH levels are moderately increased. Radioactive iodine uptake returns to normal or might be even increased due to the rise of TSH.
3. Recovery (3-4 weeks). Thyroid hormones and and TSH levels return to normal as the disease subsides.

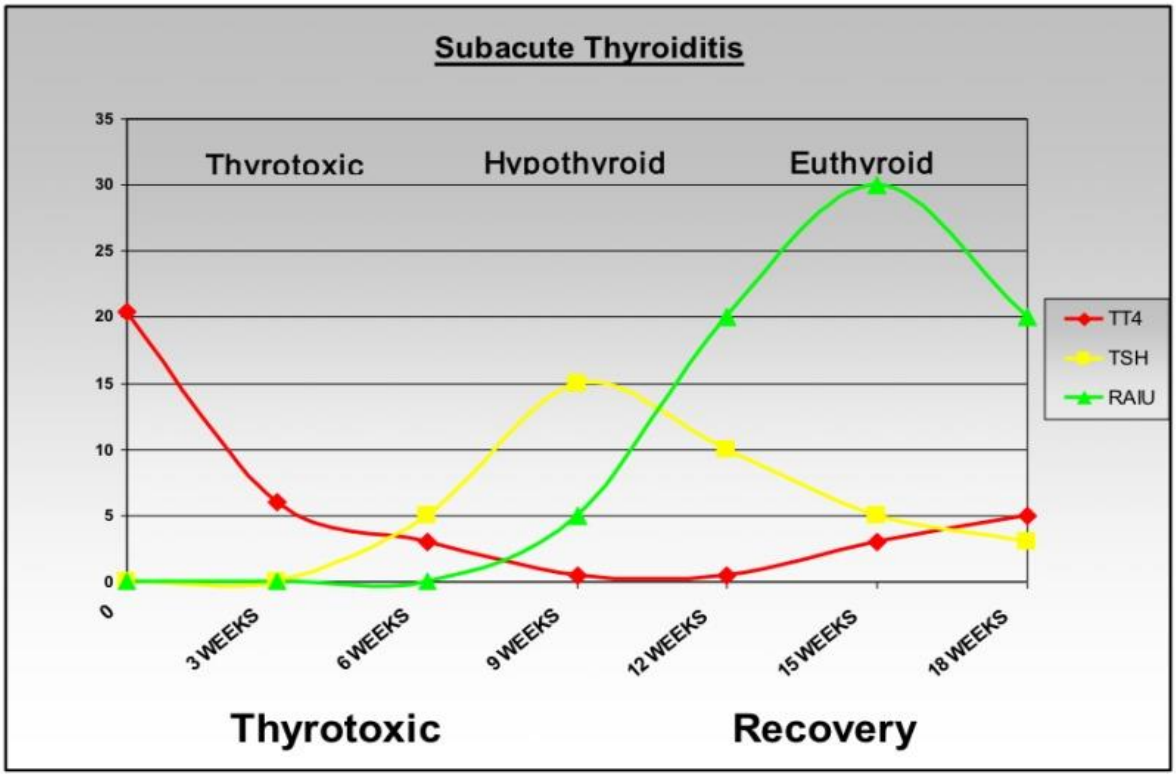


Figure 4. Time Course of Subacute Thyroiditis.

Clinical presentation includes pain in the anterior neck and fever of 37.5° to 38.5° C. Neck pain characteristically shifts from side to side and may settle in one

area, frequently radiating to the jaw and ears. It is often confused with dental pain, pharyngitis, or otitis and is aggravated by swallowing or turning of the head.

There may be signs of thyrotoxicosis or hypothyroidism depending on the phase of the disease. Clinical signs and symptoms of thyroiditis are often preceded by symptoms of upper respiratory tract infection. Sometimes the onset of the disease is sudden, acute and severe without typical foregoing symptoms. On physical examination, the thyroid is asymmetrically enlarged, firm, and tender.

The usual outcome is complete resolution, but permanent hypothyroidism can develop, especially in patients with coincidental thyroid autoimmunity or when follicular destruction is extensive.

Diagnosis is primarily clinical, based on finding an enlarged, tender thyroid in patients with the appropriate clinical history. Thyroid testing with TSH and at least a free T4 measurement is usually also done. Radioactive iodine uptake should be measured to confirm the diagnosis.

Laboratory findings early in the disease include an increase in free T4 and T3, a marked decrease in TSH and thyroid radioactive iodine uptake (often 0), high ESR and high white blood cell count. After several weeks, the thyroid is depleted of T4 and T3 stores, and transient hypothyroidism develops accompanied by a decrease in free T4 and T3, a rise in TSH, and recovery of thyroid radioactive iodine uptake. Weakly positive thyroid antibodies may be present. Measurement of free T4, T3, and TSH at 2-4-weeks intervals identifies the stages of the disease. When the diagnosis is uncertain, fine-needle aspiration biopsy is useful. Thyroid ultrasonography with color Doppler shows multiple irregular sonolucent areas and reduced blood flow in contrast with the increased flow of Grave's disease.

Treatment. Discomfort, pain in anterior neck is treated with high doses of aspirin (600 mg every 4-6 hours) or other NSAIDs. In moderately and severely symptomatic cases, corticosteroids (prednisone 40 to 60 mg per os once/day, gradually decreasing the dose over 6 to 8 weeks) eradicate all symptoms within 48

hours. If a relapse occurs during prednisone withdrawal, treatment should be started again and withdrawn more gradually. In these patients it is reasonable to wait until the radioactive iodine uptake normalizes before stopping therapy.

Mild symptoms of thyrotoxicosis improve spontaneously and don't require specific treatment. Bothersome hyperthyroid symptoms may be treated with a short course of a beta-blocker. Antithyroid drugs are useless in treatment of thyrotoxic phase. If hypothyroidism is marked or persists, thyroid hormone replacement therapy may be required, rarely permanently. The doses of L-thyroxine should be low enough to allow TSH-mediated recovery.

Hashimoto's thyroiditis

Hashimoto thyroiditis is chronic autoimmune inflammation of the thyroid gland with lymphocytic infiltration.

Hashimoto thyroiditis is the most common cause of primary hypothyroidism in the world. It is four times more prevalent among women. It is more common in certain populations, such as the Japanese, probably because of genetic factors and chronic overexposure to dietary iodine. Incidence increases with age and in patients with chromosomal disorders, such as Down syndrome, Turner syndrome, and Klinefelter syndrome. A family history of thyroid disorders is a common finding upon collecting a history.

Hashimoto thyroiditis is sometimes associated with other autoimmune disorders, including Addison disease (adrenal insufficiency), type 1 diabetes mellitus, hypoparathyroidism, vitiligo, celiac disease, premature graying of hair, connective tissue disorders (rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome), pernicious anemia, and type 2 polyglandular deficiency syndrome (Schmidt syndrome - a combination of Addison disease with hypothyroidism secondary to Hashimoto thyroiditis and/or type 1 diabetes mellitus). There may be an increased incidence of thyroid tumors, rarely thyroid lymphoma.

As it happens in other autoimmune diseases, both genetic and environmental factors work together to determine the susceptibility of a person to autoimmune thyroiditis. The proven genetic risk factors are HLA-DR polymorphisms, especially HLA-DR3, -DR4, -DR5 in whites. The female predisposition to thyroid autoimmunity is associated with sex steroid effects on the immune response; a role of X-linked genetic factor is also possible. Environmental factors include chronic exposure to high-iodine diet and viral infections.

Pathologically, there is extensive infiltration of thyroid with lymphocytes (CD4+ and CD8+ T cells, B cells), atrophy of the follicles, absence of colloid and mild to moderate scarring. There is production of antibodies to TPO and Tg, which are the important markers of thyroid autoimmunity, but possess a secondary pathogenic role as they only reinforce the ongoing autoimmune response. About 20% of patients with autoimmune thyroiditis have inhibiting antibodies against TSH receptors, which prevent the binding of TSH. These TSH receptor blocking antibodies contribute to the development of hypothyroidism and, especially in Asian patients, to thyroid atrophy.

Clinically, patients complain on painless enlargement of the thyroid or fullness in the throat. Physical examination reveals a nontender goiter that is firm; has smooth or nodular surface, and is rubberier than the normal thyroid. Many patients present with symptoms of hypothyroidism, but some present with hyperthyroidism that may be due to thyroiditis.

Hashimoto's encephalopathy has been defined as a steroid-responsive syndrome associated with TPO antibodies, myoclonus, and slow-wave activity on electroencephalography, but the relationship with thyroid autoimmunity or hypothyroidism is not established.

Lab diagnosis includes measuring T4, TSH, and thyroid autoantibodies. At the early stages of the disease, T4 and TSH levels are normal and there are high titers of thyroid peroxidase antibodies and, less commonly, of antithyroglobulin antibodies.

Later, as hypothyroidism progresses, T4 level decreases and TSH level goes up, which is characteristic of primary hypothyroidism.

Low levels of circulating antibodies are common in other thyroid diseases, such as multinodular goiter and thyroid malignancy. Antithyroid microsomal antibodies in titers greater than 1:6,400 or antithyroid peroxidase antibodies in excess of 200 IU per mL, however, are strongly suggestive of chronic autoimmune thyroiditis.

Thyroid ultrasonography should be done if there are palpable nodules. Ultrasonography often reveals that the thyroid tissue has a heterogeneous, hypoechoic echotexture with septations that form hypoechoic micronodules.

Radioactive iodine uptake can be very variable and range between decreased, normal or increased, reflecting the expanse of follicular destruction. Patchy pattern of uptake is quite common, providing little diagnostic value.

If there is any doubt about the cause of a goiter associated with hypothyroidism, fine needle aspiration biopsy can be used to confirm the presence of autoimmune thyroiditis.

Testing for other autoimmune disorders is done when clinical manifestations are present.

Many patients do not require treatment because thyroiditis is usually asymptomatic and the size of the goiter is small. However, when hypothyroidism develops, a treatment with thyroxine (T_4) is indicated. Thyroid hormone replacement therapy should also be administered in patients with a TSH level within the normal range, to reduce goiter size and prevent progression to overt hypothyroidism in high-risk patients. Lifetime replacement of L-thyroxine is recommended for hypothyroid patients, at a starting dosage of 25 to 50 mcg per day, with gradual titration to an average daily dosage of 75 to 150 mcg. A lower starting dosage (12.5 to 25 mcg per day) and a more gradual titration are recommended in elderly patients and in patients

with cardiovascular disease. The dosage might be increased in these patients 25 to 50 mcg every 1-1,5 months until normal TSH level is achieved.

In patients with subclinical hypothyroidism (elevated TSH level and a normal T_4 level), indications for treatment are less obvious. There is a high probability that the patient will develop hypothyroidism if the TSH level is greater than 20 mU/L and T_4 level is normal. Hypothyroidism will develop in 80 percent of patients if the TSH level is 10-20 mU/L and the antimicrosomal antibody titer is greater than 1:1,600. Therefore, it is recommended to initiate treatment in patients, who are symptomatic; in patients with a serum TSH level above 10 mU/L; in patients with high antibody titers (because of an increased risk of progression to hypothyroidism). Patients with a history of chronic lymphocytic thyroiditis need annual assessment of thyroid function, due to the risk of developing hypothyroidism.

Riedel's thyroiditis

Riedel's thyroiditis is a rare disorder, first described by B. Riedel in 1896. It typically occurs in middle-aged (30-60 years old) women. It presents with stealthy, painless goiter. There are local symptoms due to compression of esophagus, trachea, recurrent laryngeal nerves or neck veins. The fibrosis is very dense and can expand outside the thyroid capsule. The functional ability of thyroid gland usually remains intact. On palpation the goiter is firm, nontender, fixed and often asymmetric.

Diagnosis includes ultrasound, which reveals fibrosis of the thyroid gland, often penetrating to the capsule. TFT shows normal levels of TSH, T3 and T4. The decisive test is open biopsy (FNA biopsy is usually inadequate).

The differential diagnosis is usually made with thyroid cancer.

Treatment is surgical only and directed to relief of compressive symptoms. Tamoxifen may also be applied.

Riedel's thyroiditis is quite often associated with fibrosis of other sites – retroperitoneum, mediastinum, orbit, tongue, biliary tree.

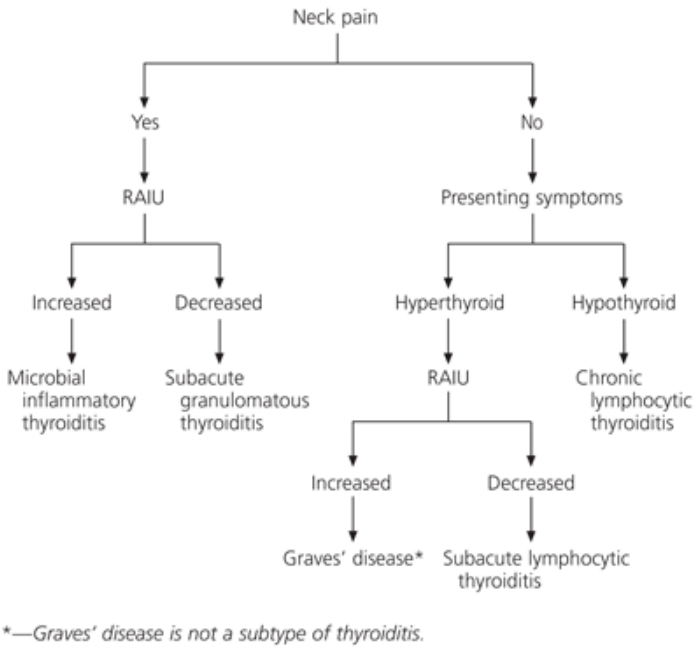


Figure 5. Algorithm for the evaluation of patients with suspected thyroiditis.

Review questions:

1. The Schmidt syndrome includes:
   A. Addison disease +hypothyroidism
   B. Addison disease + type 1 diabetes mellitus
   C. Addison disease + hypogonadism
   D. Galactorrhea + hypothyroidism
2. What criterion is the most adequate for the adjustment of L-thyroxine dose in treatment of Hashimoto's disease?
   A. Normalization of T4
   B. Normalization of TTH
   C. Reduction of size and density of thyroid gland
   D. Reduction of titers of antithyroglobulin antibodies
3. What is the most important feature of thyroid gland structure according to the results of ultrasonography in case of autoimmune thyroiditis:
   A. Echogenic density increased

B. Echogenic density decreased

C. Heterogeneous echogenic density

D. Homogeneous echogenic density

4. All listed below diseases have autoimmune origin, except of:

A. Hashimoto's thyroiditis

B. Addison’s disease

C. Diabetes mellitus type 1

D. Diabetes mellitus type 2

5. Which type of therapy is preferred in the treatment of Riedel’s thyroiditis?

A. Radioiodine treatment

B. Surgery

C. Thyroid hormone replacement

D. Systemic glucocorticoids

6. Which one of the following symptoms would be expected in a patient with a diagnosis of de Quervain thyroiditis?

A. Sudden onset of laryngitis

B. Recent lower respiratory infection

C. Dysphagia

D. Presence of large thyroid goiter

7. How can one differentiate between Graves’ disease and de Quervain thyroiditis during the hyperthyroid state?

A. By doing a radioactive iodine uptake test

B. TSH in Graves’ disease is normal

C. T4 is the best marker of Graves’ disease

D. Neck ultrasound

8. A patient is suspected of having de Quervain thyroiditis. Which of the following lab values are most likely?

A. Normal TSH, free T3, and free T4 levels

B. Elevated ESR and C-reactive protein levels

C. Elevated WBC count and positive blood cultures

D. Increased levels of anti-TPO antibodies and anti-Tg antibodies

9. What assay allows to confirm the autoimmune etiology of hypothyroidism in Hashimoto thyroiditis?

A. TFT

B. CBC with differential

C. Radioactive iodine uptake

D. Determination of anti-TPO antibodies and anti-Tg antibodies in blood

10. A patient is suspected of having Riedel's thyroiditis. Which of the following diagnostic methods will allow to discern it from thyroid cancer?

A. Radioactive iodine uptake

B. FNA biopsy

C. Open biopsy

D. Neck ultrasound

HYPERTHYROIDISM

Hyperthyroidism is characterized by elevated plasma levels of free thyroid hormones and hypermetabolism.

Hyperthyroidism is a syndrome, which results from increased synthesis and secretion of thyroid hormones (T3 and T4) from the thyroid, caused by appearance of thyroid stimulators in the blood or by autonomous thyroid hyperfunction. It can also be caused by excessive release of thyroid hormones from the thyroid gland without increased synthesis. Such release is commonly caused by the destructive changes that occur in different types of thyroiditis. Different clinical syndromes also may cause hyperthyroidism.

The most common causes of hyperthyroidism include:

- Graves' disease (toxic diffuse goiter)
- Toxic multinodular goiter
- Thyroiditis
- Single, autonomous, hyperfunctioning "hot" nodule
- Thyrotoxicosis factitia

Graves' disease (toxic diffuse goiter), the most common cause of hyperthyroidism, is characterized by hyperthyroidism, goiter, ophthalmopathy, and pretibial myxedema. Usually thyroid enlargement, goiter, and the signs of excessive thyroid hormone action are the features of the disease, but the presence of all components together or any individual component alone fits a patient within the syndrome, and patients don't need to be hyperthyroid in order to have Graves' disease. The syndrome typically consists of two major categories of phenomena. The first category is specific to Graves' disease, and is caused by the autoimmune process itself; it includes the exophthalmos, thyroid enlargement and thyroid stimulation; and the skin changes. The second category of problems is caused by the excessive thyroid hormone in blood. This thyrotoxicosis (or hyperthyroidism), does not differ from that induced by any other cause of excessive thyroid hormone (see differential diagnosis

of hyperthyroidism). Excessive thyroid hormones causes a widespread disorders in metabolism.

Pathophysiology. Graves' disease is an autoimmune disease, but the real cause of autoimmune reaction remains unclear. A strong hereditary predisposition exists. The presence of HLA antigens DR3, DQ 2, and DQA1*0501 predisposes to Graves' disease. The abnormal immune response is characterized by the production of antibodies aimed against thyroid tissue antigens, including antibodies that bind to TSH receptor. These antibodies are characterized by stimulating influence on the thyroid gland and are named the thyroid stimulating antibodies (TSAb). It was found that T-lymphocyte suppressor cell function is diminished in active Graves' disease and suppressor cell number is reduced. There is an idea that a malfunction in the control of autoimmune responses is present in this disease, which leads to production of high titers of autoantibodies that might stimulate the thyroid gland or even cause thyroid damage and cell death. Graves’ disease might accompany other autoimmune disorders, such as connective tissue disorders, type 1 diabetes mellitus, pernicious anemia, premature graying of hair vitiligo, and polyglandular deficiency syndrome.

An abnormal immune response is characterized by the presence of antibodies directed against thyroid tissue antigens, including antibodies that react with the TSH receptor by binding to the receptor. Some of these antibodies act as agonists and stimulate the thyroid gland. The best known antibodies are thyroid stimulating antibodies (TSAb). With active Graves disease, it was reported that the function of T-lymphocyte suppressor cells decreases, and the number of suppressor cells decreases. It is believed that an abnormality in the control of autoimmune reactions is present in this disease and leads to the generation of high levels of autoantibodies that can stimulate the thyroid gland or ultimately cause thyroid damage and cell death. Sometimes Graves' disease occurs with other autoimmune diseases, including type 1 diabetes, connective tissue diseases, pernicious anemia, vitiligo, premature graying of hair, and polyglandular insufficiency syndrome.

Infiltrative ophthalmopathy is responsible for the development of exophthalmos in Graves' disease. Its pathogenesis is poorly understood, but may result from production of immunoglobulins directed to the TSH receptors on the membrane of orbital fibroblasts and adipocytes that leads to release of proinflammatory cytokines, inflammation, and accumulation of glycosaminoglycans. Ophthalmopathy might occur long before the onset of hyperthyroidism or late thereafter (several years or even decades). It also possesses the ability to worsen or abate independently of the clinical course of hyperthyroidism. The development of ophthalmopathy in patient with Graves' and normal thyroid function is called euthyroid Graves' disease.

The clinical presentation may be obvious or subtle. A diffuse enlargement of thyroid gland or palpable nodule may be present.

Many typical symptoms of hyperthyroidism are analogous to those of adrenergic excess, such as irritability, nervousness, emotional lability, hyperactivity, palpitations, increased perspiration, heat hypersensitivity, fatigue, insomnia or decreased sleep requirement, weight loss (with increased appetite), weakness, tremor, and frequent bowel movements (diarrhea might develop);

Cardiac symptoms are often mentioned as "thyrotoxic heart" and include heart pounding or palpitations, ankle edema (without heart disease); less frequently, atrial fibrillation, orthopnea, paroxysmal tachycardia, anginal pain, and chronic heart failure.

Eye symptoms: prominence of eyes, pain or irritation of eyes, puffiness of lids, decreasing acuity of vision, blurred or double vision, decreased eyeball motility.

Reproductive system disorders: decrease in menstrual flow; decreased fertility, menstrual irregularity or amenorrhea.

Skin symptoms: change in texture of skin and nails, swelling over outer surface of shin, vitiligo, thinning of hair.

Other symptoms include dyspnea, polyuria, occasional bursitis. Periodic paralysis is possible, but rare.

Physical signs may include weight loss; restlessness; emotional lability; hyperkinetic thought, speech and overall behavior; lymphadenopathy and occasional splenomegaly; sometimes enlarged cervical nodes; goiter; tremor, thyroid thrill and bruit; objective muscle wasting and weakness, quickened and hypermetric reflexes.

Cardiovascular signs: overactive heart, tachycardia, widened pulse pressure; occasional cardiomegaly, signs of congestive heart failure, paroxysmal tachycardia or atrial fibrillation, tachypnea on exertion.

Eye signs include stare, eyelid retraction, eyelid lag, globe lag, prominence of eyes, and mild conjunctival injection. These signs occur because of excessive adrenergic stimulation and usually subside with successful treatment. Infiltrative ophthalmopathy is a more serious disorder. It is specific to Graves' disease and can occur long before or after hyperthyroidism. Ophthalmopathy is characterized by lacrimation, orbital pain, irritation, increased retro-orbital tissue, exophthalmos, photophobia, and lymphocytic infiltration of the extraocular muscles, which causes their weakness and can result in double vision. Also scotomata, decreased visual acuity, papilledema, retinal hemorrhage, and lid edema can be present.

Skin signs: fine, warm, moist skin, fine hair and often loss of curls, oncholysis (Plummer's nails), acropachy, pretibial myxedema, hyperpigmentation or vitiligo.

Infiltrative dermopathy (pretibial myxedema), presents with nonpitting infiltration of the pretibial area by proteinaceous ground substance. It usually occurs in the presence of infiltrative Graves ophthalmopathy. In the early stages, the shin skin is often pruritic and erythematous and becomes hyperpigmented afterwards. Infiltrative dermopathy may occur long before or after hyperthyroidism.

Thyroid storm is an acute form of hyperthyroidism, which occurs in patients with untreated or inadequately treated severe hyperthyroidism. It is a rare condition, which develops chiefly in patients with Graves' disease or toxic multinodular goiter. Toxic adenoma is a less common cause and is characterized by generally less severe manifestations. The incidence of thyroid storm currently may be as low as 0.2 cases

per 100,000 of population. Thyroid storm may be precipitated by intercurrent illness, particularly various infections (pneumonia, upper respiratory tract infection, enteric infections, or any other infection), surgery, trauma, stroke, myocardial infarction, embolism, preeclampsia, or diabetic ketoacidosis.

Thyroid storm presents with bright and drastic symptoms of hyperthyroidism with one or more of the following: marked weakness and muscle wasting, fever (39-41°C), tachycardia (usually above 130 beats per minute), tremor, extreme restlessness with broad emotional swings, agitation/psychosis confusion, nausea, vomiting, diarrhea and coma. Cardiovascular collapse and shock may also develop.

Rarely, thyroid storm can look dramatically different. This form is called apathetic storm, which is characterized by emotional apathy, extreme weakness, and confusion. Fever is low or absent.

Signs and symptoms of decompensation in organ systems may be present. Congestive heart failure might develop, with congestive hepatomegaly, peripheral edema, and respiratory distress. Heart rhythm disorders are common, such as marked sinus tachycardia or some tachyarrhythmias (atrial fibrillation). Liver damage and jaundice may result from congestive heart failure or the direct action of thyroid hormone on the liver. Dehydration and prerenal azotemia may occur in patients whose thyroid storm is accompanied by high fever and vomiting. Abdominal pain may be a leading feature in some cases. The clinical presentation may be veiled by a secondary infection.

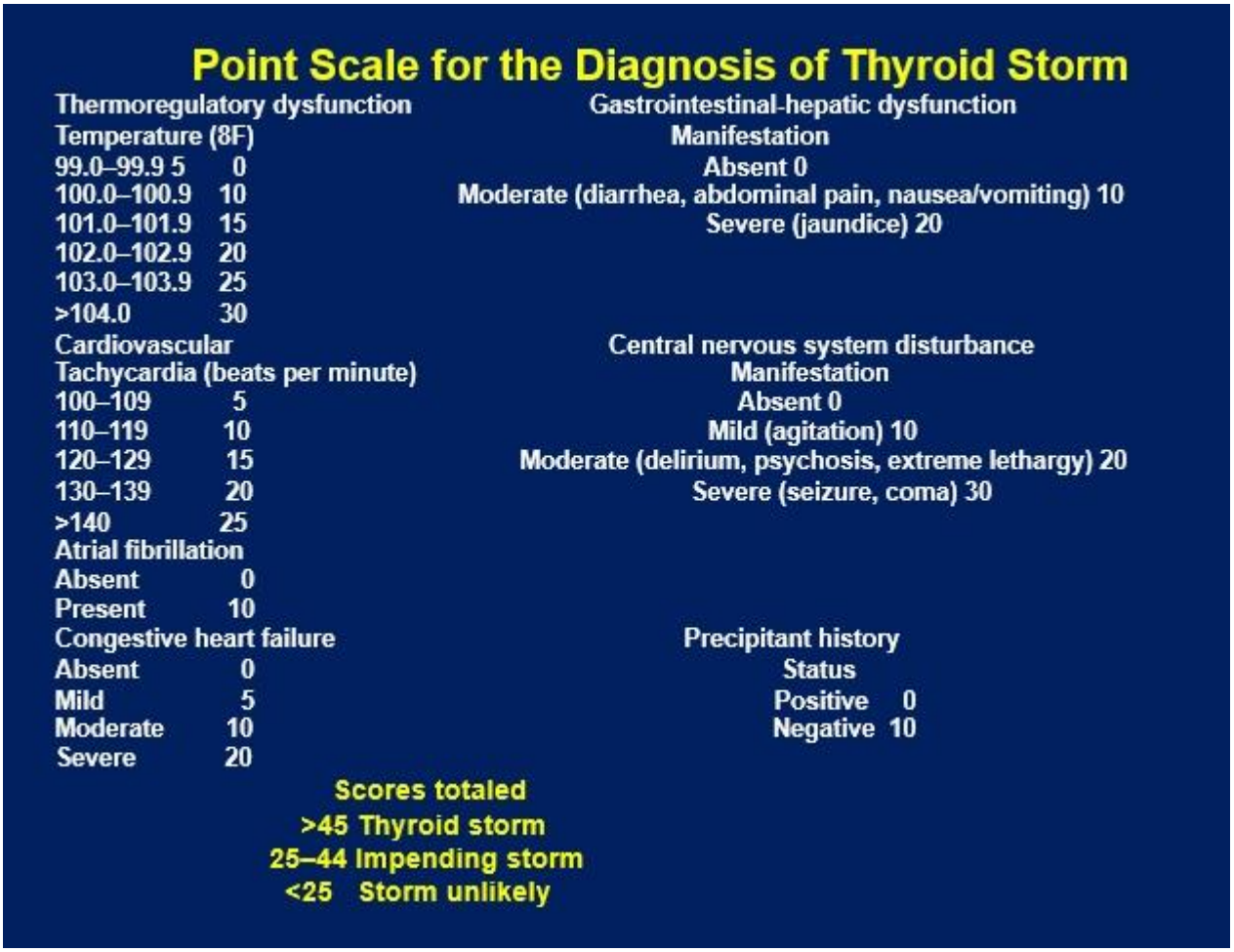


Figure 6. Burch-Wartofsky Point Scale for the Diagnosis of Thyroid Storm.

Diagnosis of hyperthyroidism is made by collecting history, performing physical examination, and obtaining thyroid function tests. Serum TSH measurement is the most informative test, because TSH is suppressed in hyperthyroid patients. TSH may be as low as 0 - 1 μU/ml in severe thyrotoxicosis, although values of 1 - 3 are possible in patients with mild disease, especially in older patients with smoldering toxic multinodular goiter. TSH can be elevated in the rare cases when hyperthyroidism is caused by TSH-secreting pituitary adenoma or pituitary resistance to the inhibition by thyroid hormone.

Free T4 level is elevated in hyperthyroidism. The degree of free T4 increase above normal ranges provides an evaluation of the disease severity. However, in some cases T4 can be falsely normal in patients with true hyperthyroidism. Such situation

may occur in patients with severe systemic illness; depressed serum levels of T4 - binding protein; T3 toxicosis. If patient has subtle symptoms and signs of hyperthyroidism, normal free T4 level and low TSH, then serum T3 should be measured to reveal T3 toxicosis; an elevated level confirms the diagnosis.

The cause of hyperthyroidism can often be diagnosed clinically: for example, if there is a history of exposure to a drug, or the presence of signs specific to Graves' disease. Radioactive iodine uptake by the thyroid gland may be helpful for the detection of a cause; it is measured by using ^{123}I. Radioactive iodine uptake by the thyroid is usually elevated when hyperthyroidism occurs due to hormone overproduction. In contrary, radioactive iodine uptake is low when hyperthyroidism is due to thyroiditis, ectopic hormone production, or iodine ingestion.

Antibodies to TSH receptor can be measured to reveal Graves' disease. The measurement is performed in pregnant women with a history of Graves' disease in the 3rd trimester of pregnancy to assess the risk of Graves' disease in newborns. Antibodies to the TSH receptor easily cross the placenta to stimulate the fetal thyroid. Most patients with Graves' disease are characterized by the presence of circulating antithyroid peroxidase antibodies, and a small number of them have antithyroglobulin antibodies. Positive Tg antibody tests are typical for thyroiditis. Positive tests confirm autoimmunity. Negative tests are seen in patients with causes of thyrotoxicosis other than Graves' disease.

Antibodies to TSH-Receptor-Thyrotropin receptor antibody (TRAb) assays have become readily available, and a positive result strongly supports the diagnosis of Graves' disease. Determination of TRAb is not required for the diagnosis, but the implied specificity of a positive test provides security in diagnosis, and for this reason the assay is now widely used. The assay is valuable as another supporting fact in establishing the cause of exophthalmos, in the absence of thyrotoxicosis.

Inappropriate TSH secretion is uncommon. The diagnosis is confirmed when hyperthyroidism occurs with elevated circulating free T4 and T3 concentrations and normal or elevated serum TSH.

If thyrotoxicosis factitia is suspected, serum thyroglobulin can be measured; it is usually low or low-normal—unlike in all other causes of hyperthyroidism.

Differential diagnosis for hyperthyroidism

Toxic multinodular goiter is usually distinguished by careful physical examination and a history of goiter for many years before symptoms of hyperthyroidism developed. The thyrotoxicosis comes on insidiously, and often, in the older people usually afflicted, symptoms may be mild, or suggest another problem such as heart disease. The thyroid scan may be diagnostic, showing areas of increased and decreased isotope uptake. The results of assays for antithyroid antibodies, including TRAb, are usually negative. TMNG is typically produced by activating somatic mutations in TSH-R in one or more nodules, allowing them to enlarge and become functional even in the absence of TSH stimulation.

Thyrotoxicosis factitia-thyrotoxicosis may be caused by taking T4 or its analogs, most commonly due to administration of excessive replacement hormone by the patient's physician. Hormone may be taken surreptitiously by the patient for weight loss or psychologic reasons. The typical findings are a normal or small thyroid gland, a low131-I uptake, a low serum TG, and, of course, a striking lack of response to antithyroid drug therapy. The problem can easily be confused with "painless thyroiditis", but in thyrotoxicosis factitia, the gland is typically small.

Hyperfunctioning solitary adenoma is suggested on the physical finding of a palpable nodule in an otherwise normal gland, and is proved by a scintiscan demonstrating preferential radioisotope accumulation in the nodule. This type of adenoma must be differentiated from congenital absence of one of the lobes of the thyroid. Toxic nodules typically present in adults with gradually developing hyperthyroidism and a nodule > 3 cm in size. These nodules are usually caused by

activating somatic mutations in the TSH-R, which endows them with mildly increased function, compared to normal tissue, even in the absence of TSH. These nodules are usually, but not always, monoclonal. In adults toxic nodules are very rarely malignant. Rarely, functioning thyroid carcinomas produce thyrotoxicosis. The diagnosis is made by the history, absence of the normal thyroid, and usually widespread functioning metastasis in lung or bones. Invasion of the gland by lymphoma has produced thyrotoxicosis, presumably due to thyroid destruction.

TSH secreting pituitary adenoma is rare and is usually missed unless one measures the plasma TSH level, or until the enlargement is sufficient to produce deficiencies in other pituitary hormones, optic chiasm pressure symptoms, or expansion of the sella turcica. These patients have thyrotoxicosis with inappropriately elevated TSH levels and may/or may not secrete more TSH after TRH stimulation. The characteristic finding is a normal or elevated TSH, and an elevated TSH alpha subunit level in blood, measured by special immunoassay. Thyrotropin receptor antibodies are not present. Exophthalmos and antibodies of Graves' disease are absent. Family history is sometimes positive for a similar condition. Demonstration of a suppressed TSH level excludes these rare cases.

Subacute thyroiditis - thyrotoxicosis is usually mild and transient, and the patient lacks the physical findings of long-standing thyrotoxicosis. If thyrotoxicosis is found in conjunction with a painful goiter and low or absent 131-I uptake, this diagnosis is likely. Usually the erythrocyte sedimentation rate (ESR) and CRP are greatly elevated, and the leukocyte count may also be increased. Occasionally the goiter is non-tender. Antibody titers are low or negative.

Administration of **large amounts of iodide** in medicines, for X-ray examinations, or in foods can occasionally precipitate thyrotoxicosis in patients with multinodular goiter or functioning adenomas. This history is important to consider since the illness may be self-limiting. Induction of thyrotoxicosis has also been observed in apparently normal individuals following prolonged exposure to organic

iodide containing compounds such as antiseptic soaps and amiodarone. **Amiodarone** is of special importance since the clinical problem often is the presentation of thyrotoxicosis in a patient with serious cardiac disease including arythmia. Amodarone can induce thyrotoxicosis in patients without known prior thyroid disease, or with multinodular goiter. The illness appears to come in two forms. In one the RAIU may be low or normal. In the second variety, which appears to be more of a thyroiditis-like syndrome, the RAIU is very suppressed, and IL-6 may be elevated. In either case TSH is suppressed, free thyroxine index may be normal or elevated, but T3 is elevated if the patient is toxic. Antibodies are usually negative.

Metastatic thyroid cancer is a possible cause. Overproduction of thyroid hormone occurs rarely from functioning metastatic follicular carcinoma, especially in pulmonary metastases.

Nonautoimmune autosomal dominant hyperthyroidism manifests during infancy. It results from mutations in the TSH receptor gene that produces continuous thyroid stimulation.

Struma ovarii develops when ovarian teratomas contain enough thyroid tissue to cause true hyperthyroidism. Radioactive iodine uptake occurs in the pelvis, and uptake by the thyroid is usually suppressed.

Treatment

Treatment of hyperthyroidism depends on cause. No single approach is optimal and patients may require multiple treatments to achieve remission. The possible options to choose from include the following:

- Antithyroid drugs
- Beta-blockers
- Iodine
- Radioactive iodine
- Surgery

The mechanism of action of **antithyroid drugs** involves blocking of thyroid peroxidase, decreasing the organification of iodide, and impairment of the coupling reaction. They also reduce thyroid antibody levels by mechanisms that remain unclear. Antithyroid drugs are represented with propylthiouracil and methimazole. About 20 to 50% of patients with Graves' disease remain in remission after a 1-2 year course of either drug. The return to normal or a marked decrease in gland size, the restoration of a normal serum TSH level, and less severe hyperthyroidism before therapy are good prognostic signs of long-term remission.

Toxic nodular goiter rarely goes into remission with pharmacological therapy alone, therefore antithyroid drugsare given only in preparation for surgical treatment or ^{131}I therapy.

Propylthiouracil. In addition to mentioned above mechanism of action, propylthiouracil in high doses also inhibits the peripheral conversion of T4 to T3.Because of the increased risk of severe hepatic failure in some patients < 40, especially teenagers and young adults, propylthiouracil is now recommended only in special situations (in the 1st trimester of pregnancy, in thyroid storm).The usual starting dosage of propylthiouracil is 100 to 150 mg per os every 8 hours and the dosage is tapered down (as thyrotoxicosis improves) to 50 mg 2-3 times a day.Usually,control is achieved in 2 to 3 months. More rapid control can be achieved by increasing the dosage of propylthiouracil to 150 to 200 mg every 8 hours. Such dosages or higher ones (up to 400 mg every 8 hours) are generally reserved for severely ill patients, including those with thyroid storm, to block the conversion of T4 to T3.The combination of high-dose propylthiouracil and dexamethasone, also a potent inhibitor of T4 to T3 conversion, can relieve symptoms of severe hyperthyroidism and restore the serum T3 level to normal within a week.

Currently, *methimazole* is the preferred drug. The usual starting dosage of methimazole is 5 to 20 mg per os three times a day. When T4 and T3 levels normalize, the dosage is decreased to the lowest effective amount,

usually methimazole 2.5 to 10 mg once/day. Maintenance doses of methimazole can be continued for one or many years depending on the clinical circumstances. At this point, methimazole need only be given once a day, which improves adherence. Carbimazole, which is used widely in Europe, is rapidly converted to methimazole. The usual starting dose is similar to that of methimazole; maintenance dosage is 2.5 to 10 mg per os once/day or 2.5 to 5 mg twice a day. Maximum remission rates (up to 30-50%) are achieved by 18-24 months. Patients with severe hyperthyroidism and large goiters are most likely to relapse when treatment stops, but outcomes are difficult to predict. All patients should be followed closely for relapse during the first year after treatment and annually thereafter.

Side effects include rash, allergic reactions, arthralgia, abnormal liver function (including hepatic failure with propylthiouracil), systemic lupus erythematosus-like syndrome, and, in about 0.1% of patients, reversible agranulocytosis. Patients allergic to one drug can be switched to the other, but cross-sensitivity may occur. If agranulocytosis occurs, the patient cannot be switched to the other drug; other therapy (radioiodine, surgery) should be used. Patients should be aware of agranulocytosis symptoms (e.g., sore throat, fever, mouth ulcers). Complete blood count confirms the diagnosis. There is no need to monitor blood counts prospectively, because the onset of agranulocytosis is idiosyncratic and abrupt. When methimazole is used in dosages less than 20 mg/day, agranulocytosis is less common; with propylthiouracil, agranulocytosis may occur at any dosage.

In a very rare cases, methimazole has been associated with embryopathy, scalp and gastrointestinal defects in neonates. Because of these complications, propylthiouracil is used in the first trimester of pregnancy.

Beta-blockers may be helpful to control adrenergic symptoms, especially in the early stages, before antithyroid drugs take effect. Manifestations typically responding to beta-blockers: tachycardia, tremor, mental symptoms, eyelid lag; occasionally heat intolerance and sweating, diarrhea, proximal myopathy. Propranolol is given 20-40

mg every 6 hours, but up to 200 mg every six hours may be needed. Longer-acting beta-blockers such as atenolol and metoprolol can also be used.

Propranolol is indicated in thyroid storm. In this case it may be given intravenously (1 - 3 mg, rarely up to 6 mg) over 3 - 10 minutes and repeated every four to six hours under electrocardiographic control. It rapidly decreases heart rate, usually within 2 to 3 hours when given orally and within minutes when given IV. Esmolol should be used in the intensive care unit because it requires careful titration and monitoring. Beta-blockers are also indicated for tachycardia with hyperthyroidism, especially in elderly patients.

The drug must be used with caution when there is evidence of severe thyrotoxicosis, or heart failure, but often control of tachycardia permits improved circulation. Beta blockade can induce cardiovascular collapse in patients with or without heart failure, and asystolic arrest. Calcium channel blockers may control tachyarrhythmias in patients in whom beta-blockers are contraindicated.

Iodine in therapeutic doses inhibits the release of T3 and T4 within few hours. It also inhibits the organification of iodine - a transitory effect lasting from a few days to one week, after which inhibition usually ceases. Indications for the usage of iodine: emergency management of thyroid storm; hyperthyroid patients undergoing emergency nonthyroid surgery; preoperative preparation of hyperthyroid patients undergoing thyroidectomy (because of its ability to decrease the vascularity of the thyroid). Iodine generally is not used for routine treatment of hyperthyroidism. The usual dosage is 2 to 3 drops (100 to 150 mg) of a saturated potassium iodide solution per os 3-4 times a day or sodium iodide0.5 to 1 g in 1 liter of 0.9% saline solution IV given slowly once a day. Combined dexamethasone, potassium iodide, and propylthiouracil can lower the serum T3 level to normal in 24 hours, which is useful in severe thyrotoxicosis. Complications of iodine therapy include inflammation of the salivary glands, conjunctivitis, and rash.

Radioactive iodine(RAI) causes progressive destruction of thyroid cells. In some countries, radioiodine is the most common treatment for hyperthyroidism, because it is a quick, easy, moderately expensive method, which allows avoiding surgery, and has no significant risk in adults. Therefore,^{131}I is often recommended as the treatment of choice for Graves' disease and toxic nodular goiter in adult patients.

Indications and contraindications for RAI therapy.

Indications:

- Age above 18 years old
- Patients who fail to respond to antithyroid drugs
- Prior thyroid or other neck surgery
- Contraindications to surgery, such as severe heart, lung,or renal disease
- Women intending to become pregnant (more than 6 months later)

Contraindications:

- Pregnancy or lactation
- Insufficient ^{131}I uptake due to prior medication or disease
- Suspicion of thyroid malignancy
- Age below 18 years old
- Patient concerns regarding radiation exposure
- Unusually large glands
- Active exophthalmos

Dosage of ^{131}I is difficult to adjust because the response of the gland cannot be predicted; some physicians give a standard dose of 8 to 15 microCuries (mCi). Others calculate the dose based on estimated thyroid size and the 24-h uptake to give a dose of 80 to 120 mCi per gramof thyroid tissue.

When sufficient ^{131}I is given to cause euthyroidism, about 25 to 50% of patients become hypothyroid 1 year later, and the incidence continues to increase yearly. Thus, most patients eventually become hypothyroid. However, if smaller doses are

used, incidence of recurrence is higher. Larger doses, such as 10 to 20 mCi, often cause hypothyroidism within 6 months, and thus ablative therapy with ^{131}I has become the preferred approach.

Radioactive iodine is not used during lactation because it can enter breast milk and cause hypothyroidism in the infant. It is not used during pregnancy because it crosses the placenta and can cause severe fetal hypothyroidism. There is no proof that radioiodine increases the incidence of tumors, leukemia, thyroid cancer, or birth defects in children born to previously hyperthyroid women who become pregnant later in life.

The short-term side effects of ^{131}I therapy are typically minimal. A transient exacerbation of thyrotoxicosis can occur; also an apparent thyroid storm can be induced within several days after ^{131}I therapy. Few patients develop mild pain and tenderness over the thyroid gland and, rarely, dysphagia. Some patients develop temporary hair loss, which occurs two to three months after therapy.

Certain radiation safety precautions should be taken in the first few days after the radioiodine treatment: patients should avoid close prolonged contact with children and pregnant women because of possible transmission of residual isotope and excessive exposure to radiation emanating from the gland.

Surgery. Subtotal thyroidectomy is an established and effective form of therapy for Graves' disease, if the patient has been suitably prepared for surgery.

The major advantage of surgery is that definitive management is often obtained over an 8-12 -week period, including preoperative medical control, and many patients are euthyroid after operation. Its well-known disadvantages include expense, surgery itself, and the risks of recurrent nerve and parathyroid damage, hypothyroidism, and recurrence. However, if a competent surgeon is available, surgical management may be used as the primary or secondary therapy in many young adults. The indications for surgery as the secondary therapy include: noresponse to prolonged antithyroid drug therapy; development of toxic reactions to the drugs; patients who are unsuitable

for ^{131}I therapy; patients with huge glands, which frequently do not regress adequately after ^{131}I therapy; children, poorly controlled on antithyroid drugs. The indications for surgery as the primary therapyinclude: pregnant women requiring excessive doses of antithyroid drugs; patients with significant exophthalmos; patients with coincident thyroid nodules that are suspicious of carcinoma.

Early total thyroidectomy has been recommended for treating older, chronically ill patients with thyrotoxic storm if high-dose propilthiouracil treatment, iodine, and glucocorticoids fail to improve the patient's condition within 12 – 24 hours. Total thyroidectomy may also be preferred in patients with serious eye disease or high TSH receptor antibody levels, in order to ease the eye disease and to decrease the incidence of recurrence.

The contraindications to surgery include previous thyroid surgery, severe coincident heart or lung disease, the lack of a qualified surgeon, and pregnancy in the third trimester, since anesthesia and surgery may induce premature labor.

If subtotal throidectomy has been performed, thyroid hormone replacement may not be needed. In 50-70% of patients, the residual gland is able to form enough hormone to prevent even transient clinical hypothyroidism. Serum hormone levels should be determined every two to four months until it is clear that the patient does not need replacement. If total thyroidectomy has been performed, full replacement doses of thyroxine (1.7 mcg/kg of body weight) should be instituted immediately, and T4 levels checked in about 2 weeks for adjustment.

Immunosuppressive Therapy. The development of new targeted and relatively safe immune suppressive treatments has allowed their usagein Graves' disease. Rituximab, an anti CD20 B-cell lymphocyte depleting monoclonal antibody, was initially found to induce remission in Graves ophthalmopathy. It also mediates decreases in anti-thyroid antibodies, and is currently employed in a Phase II trial for therapy of mild, relapsing Graves' disease. Significant adverse events during therapy with rituximab have been reported: "serum sickness", mild colitis, iridocyclitis,

polyarthritis, which will probably limit its usefulness. Use of agents of this type, that work by increasing function of regulatory T cells, will probably become common in the next few years.

Treatment of thyroid storm. Thyroid storm is a life-threatening emergency requiring prompt treatment. Admission to an intensive care unit is usually required. Treatment of underlying disorder, such as infection should be performed.

Supportive measures:

- Rest
- Mild sedation
- Fluid and electrolyte replacement
- Nutritional support
- Oxygen therapy
- Nonspecific therapy as indicated
- Antibiotics
- Cardio-support as indicated
- Cooling, provided by cooling blankets and acetaminophen

Specific therapy:

- Propranolol (20 to 200 mg orally every 6 hours, or 1 to 3 mg intravenously every 4 to 6 hours. Treatment should be started with low doses, since administration of beta-blockers to patients with severe thyrotoxicosis has been associated with vascular collapse. Esmolol, a short-acting beta blocker, at a loading dose of 250 mcg/kg to 500 mcg/kg followed by 50 mcg/kg to 100 mcg/kg/minute can be used in an intensive care unit setting. For patients with reactive airway disease, a cardioselective beta blocker like atenolol or metoprolol can be employed.
- Antithyroid drugs (Propylthiouracil 500–1000mg load, then 250 mg every 4 hours or Methimazole 60-80mg/day), then taper as condition improves

- Potassium iodide (one hour after first dose of antithyroid drugs): 250mg orally every 6 hours
- Dexamethasone 2 mg every 6 hours or hydrocortisone 300mg intravenous load, then 100mg every 8 hours.

Second Line Therapy

- Ipodate (Oragrafin) or other iodinated contrast agents (inhibit peripheral T4 to T3 conversion)
- Plasmapheresis (can remove circulating thyroid hormone and rapidly decrease thyroid hormone levels)
- Oral T4 and T3 binding resins- colestipol or cholestyramine (can trap thyroid hormone in the intestine and prevent recirculation)
- Dialysis
- Lithium in patients who cannot take iodine
- Definitive therapy after control of the crisis via ablation of the thyroid with ^{131}I or surgical treatment

Treatment of infiltrative ophthalmopathy and dermopathy.

Ophthalmopathy should be treated jointly by the endocrinologist/thyroidologist and ophthalmologist. The treatment strategy includes application of selenium, corticosteroids, orbital radiation, and surgery.

Radioiodine therapy may accelerate progression of ophthalmopathy, when applied in active phase of the disease. ^{131}I therapy causes an increase in titers of TSH receptor antibody levels, and anti-Tg or TPO antibodies, which reflects an activation of autoimmunity. It perhaps is due to release of thyroid antigens by cell damage, and probably destruction of intrathyroidal T cells. Many endocrinologists are convinced that ^{131}I therapy can lead to exacerbation of infiltrative ophthalmopathy and worsening of exophthalmos in nearly 25% of patients because of this immunologic response. To compare, surgery is followed by worsening of ophthalmopathy in about

10-13%. Therefore, patients with significant ophthalmopathy may receive corticosteroids along with ^{131}I. The recommended dose of prednisolone is 30 mg/day for one month, tapering then over 2-3 months.

Pulse therapy with IV methylprednisolone can be used in case of severe ophthalmopathy (500-1000 mg of methylprednisolone in 250 ml of saline infused over 2 hours daily for 1 week, followed by oral regimen). When glucocorticoids are ineffective, orbital decompression can be achieved by removing bone from any wall of the orbit, thus allowing displacement of fat and swollen extraocular muscles. The transantral route is used most often, because it requires no external incision. Proptosis improves on average of 5 mm, but diplopia can stay or become even worse. After stabilization of eye disease, surgery must be done to correct the appearance and to cure the diplopia.

Orbital radiation has been used for many years, but the efficacy of this therapy remains unclear. Therefore, it is reserved for patients, who don't tolerate of have failed glucocorticoid therapy.

Total thyroidectomy should be considered for patients with serious active ophthalmopathy. Operative removal of the thyroid gland is followed by gradual decreaseof TSH receptor antibodies.

Biological therapies (rituximab)were recently found to induce remission in Graves' ophthalmopathy.

In case of infiltrative dermopathy, caused by Graves' disease, topical corticosteroids or corticosteroid injections into the lesions may decrease the skin lesions. Dermopathy sometimes remits spontaneously after months or years. Octreotide may be beneficial in some cases.

Subclinical hyperthyroidism

Nowadays, thyrotoxicosis is not only a clinical but also a laboratory diagnosis. Subclinical hyperthyroidism is low serum TSH in patients with normal serum free T4 and T3 and absent or minimal symptoms of hyperthyroidism.

Subclinical hyperthyroidism is far less common than subclinical hypothyroidism.

Many patients with subclinical hyperthyroidism are taking L-thyroxine. The other causes of subclinical hyperthyroidism are the same as those for clinically apparent hyperthyroidism.

Patients with serum TSH < 0.1 mU/L have an increased incidence of atrial fibrillation (particularly elderly patients), reduced bone mineral density, increased fractures, and increased mortality. Patients with serum TSH that is only slightly below normal are less likely to have these features.

In patients with subclinical hyperthyroidism who are taking L-thyroxine, reduction of the dose is the most appropriate management unless therapy is aimed at maintaining suppressed TSH levels in patients with thyroid cancer.

Therapy is indicated for patients with endogenous subclinical hyperthyroidism (serum TSH < 0.1 mU/L), especially those with atrial fibrillation or reduced bone mineral density. The usual treatment is ^{131}I, but low doses of methimazole are also effective.

Antithyroid drug treatment of patients with subclinical hyperthyroidism was found to result in a decrease in heart rate, decrease in number of atrial and ventricular premature beats, a reduction of the left ventricular mass index, and left ventricular posterior wall thickness, as well as a reduction in diastolic peak flow velocity. These changes are considered an argument for early treatment of subclinical hyperthyroidism. Subclinical hyperthyroidism may disappear or evolve into Graves hyperthyroidism, or when caused by multinodular goiter, persist for long periods unchanged.

Hyperthyroidism and insulin resistance.

Hyperthyroidisminduces a hypermetabolic state in a human body. In order to adapt to the greater energy loss, both baseline and insulin-stimulated rate of cellular glucose depletion increases as a result of the more intense glucose oxidation and lactic acid formation, the latter of which is subsequently used by the liver to accelerate gluconeogenesis and the production of endogenous glucose.

Clinical hyperthyroidism is often accompanied by glucose intolerance and insulin resistance. Glucose intolerance is observed approximately in 50% of patients with hyperthyroidism, and 2–3% of patients have diabetes. In non-diabetic subjects, normal or increased fasting insulin, peptide C and proinsulin concentrations are observed, which is indicative of moderate peripheral insulin resistance. This is associated with an increased insulin resistance in the liver, aggravation of general peripheral insulin resistance, and increased glucose uptake in muscles.

Overt hyperthyroidism increases the demand for insulin. It is associated with accelerated metabolism, tissue resistance to insulin and increased insulin degradation. In thyrotoxicosis, increased glucose absorption occurs in the digestive tract thanks to a higher rate of stomach emptying and increased blood flow in the portal vein, which leads to postprandial hyperglycemia, characteristic of hyperthyroidism.

The effect of thyroid hormones on hepatocytes is antagonistic to insulin and stimulates glucose production in the liver (increases gluconeogenesis and glycogenolysis). Thyrotoxicosis increases the production of endogenous glucose in the liver in baseline conditions (fasting state) and decreases the hepatic sensitivity to insulin. Thyroid hormones may have both a direct and an indirect effect on hepatic cells. The direct effect is achieved via alteration of transcription and translation of the genes responsible for gluconeogenesis and glycogen metabolism. Another mechanism by which thyroid hormones stimulate hepatic glucose production is based on the increased expression of the GLUT2 glucose transporter on hepatocyte plasma membranes. The indirect effect is achieved by increasing the activity of the

parasympathetic nervous system, modulated by the hypothalamus, and its influence on hepatocytes.

Moreover, thyroid hormones promote lipolysis, thereby increasing the concentration of free fatty acids in blood and accelerating insulin degradation. In thyrotoxicosis, the high levels of free T3 directly stimulate gluconeogenesis as a result of the increased activity of phosphoenolpyruvate carboxykinase.

In subjects with hyperthyroidism, lower peripheral tissue sensitivity to insulin and abnormal insulin secretion are also responsible for glucose metabolism disorders. Explaining the effect of hyperthyroidism on glucose utilisation in peripheral tissues is difficult due to the complexity of the problem. On the one hand, it was observed that the glucose uptake rate in peripheral tissues is increased by thyroid hormones, which suggests that glucose utilisation is considerably higher, especially in skeletal muscles. This increased glucose utilisation is caused mainly by the higher level of glucose oxidation stimulated by insulin. On the other hand, it has also been observed that anaerobic glucose metabolism stimulated by insulin is inhibited, as glycogenogenesis decreases due to the 'redirection' of intracellular glucose to the process of glycolysis and generation of lactic acid. The lactic acid released from peripheral cells returns to the liver, where it becomes a substrate for the increased hepatic glucose production. The occurrence of glucose intolerance associated with hyperthyroidism may be explained simply by the hepatic type of insulin resistance.

Alternatively, peripheral insulin resistance in hyperthyroidism may be explained by the increased secretion of bioactive mediators (adiponectins), such as interleukin-6 and TNF-alpha, by adipocytes. Higher levels of these adiponectins have been observed in women with hyperthyroidism.

In case of hyperthyroidism, blood insulin levels may be variable: low, normal or even high. However, majority of scientific data indicates an increased degradation of insulin in hyperthyroidism. It is also suggested that in long-term severe thyrotoxicosis, irreversible damage to the pancreas may occur.

Subclinical hyperthyroidism is defined as decreased TSH levels accompanied by normal levels of free T3 and free T4. This state is characterized by significantly lower insulin sensitivity. The increased HOMA index and the decreased Matsuda and Belfiore indices in patients with clinical and subclinical hyperthyroidism, compared to euthyroid patients, suggest that insulin resistance is present in either fasting or postprandial state. It was also determined that insignificantly (slightly) lower levels of thyroid hormones within the physiological range negatively correlate with the HOMA index. This suggests that even small deviations from thyroid hormone balance may lead to insulin resistance.

Review questions:

1. The hyperfunction of the thyroid gland in diffuse toxic goiter is associated with:
   A. Hypersecretion of TSH
   B. Hypersecretion of thyroliberin
   C. Hyperproduction of thyroid stimulating antibodies
   D. Tissue hypersensitivity to hormones
2. What should be the duration of antithyroid drug therapy in case of diffuse toxic goiter in order to achieve and maintain euthyroid state?
   A. 3 months
   B. 6 months
   C. 1 - 1,5 years
   D. Lifetime
3. What are the complications of treatment with propilthiouracil?
   A. Allergic reactions
   B. Agranulocytosis
   C. Hepatic failure
   D. All of the above

4. Lesions of cardiovascular system in hyperthyroidism are characterized by:
   A. Stable sinus tachycardia
   B. Frequent episodes of atrial fibrillation
   C. Development of heart failure
   D. All of the above.
5. What is necessary to prescribe in case of active infiltrative ophthalmopathy:
   A. Methimazole
   B. Iodine preparations
   C. Glucocorticosteroids
   D. β-blockers
6. What are the common changes of complete blood count test in diffuse toxic goiter?
   A. Leukopenia;
   B. Accelerated erythrocyte sedimentation rate;
   C. Lymphocytosis;
   D. all of the mentioned above
7. What determines the severity of thyrotoxicosis?
   A. Enlargement of goiter
   B. Degree of tachycardia
   C. Degree of body mass loss
   D. Degree of exophthalmos
8. What is the most common antithyroid drug that is used for the pharmacological therapy of hyperthyroidism?
   A. Methimazole
   B. Propilthiouracil
   C. Prednisolone
   D. Potassium iodide

9. Which of the following diseases is the most common cause for hyperthyroidism?
   A. Toxic solitary adenoma
   B. Subacute thyroiditis
   C. Diffuse toxic goiter
   D. Multinodular toxic goiter
10. What drugs may be helpful to control adrenergic symptoms, especially in the early stages of hyperthyroidism, before antithyroid drugs take effect?
   A. Dexamethasone
   B. Beta-blocker
   C. Potassium iodide
   D. Antibiotic

THYROID CANCER

Thyroid carcinoma is the most common malignancy of the endocrine system. The annual incidence of thyroid cancer varies considerably in different registries, ranging from 1.2-2.6 per 100,000 individuals in men and from 2.0-3.8 per 100,000 in women.

Differentiated tumors, such as papillary thyroid cancer or follicular thyroid cancer histologically resemble normal thyroid tissue and possess differentiated function (for example, thyroglobulin secretion is preserved). These cancers are often curable and the prognosis is good for patients, identified at early stage disease.

Undifferentiated tumors, such as anaplastic and metastatic medullary carcinoma, are aggressive, respond poorly to treatment, and are associated with bad prognosis.

The risk factors for thyroid carcinoma in patients with thyroid nodule include the following:

- History of head and neck irradiation
- Increased nodule size (over 4 cm in diameter)
- Age below 20 or above 45 years
- New or quickly enlarging neck mass
- Family history of thyroid cancer
- Nodule fixed to adjacent tissues
- Extrathyroidal extension
- Vocal cord paralysis
- Suspected lymph node involvement
- Exposure to iodine deficiency (follicular cancer)

Thyroid carcinomas are monoclonal because of persistent growth of the progeny of one cell which has somehow escaped the mechanisms which maintain normal cell division. In addition to increased rates of proliferation, some thyroid cancers exhibit impaired apoptosis and features that enhance invasion, angiogenesis and metastasis.

The process of oncogenesis is conceived to be a series of events induced by genetic and environmental factors which alter growth control. External radiation may predispose to chromosomal breaks, leading to genetic rearrangements and loss of tumor-suppressor genes. Radiation exposure increases the risk of benign and malignant thyroid nodules, and is associated with multicentric cancers. It also shifts the incidence of thyroid cancer to earlier age group.

More than 30 "oncogenes" have been recognized in the human genome. These genes are normally silent, but can become activated by chromosomal translocations, deletions, or mutations, and then can "transform" normal cells into a condition of uncontrolled growth. In general, these genes, when turned on, promote cell growth and cell division and depress differentiation. Typically, activation of one such gene may not be enough to produce malignancy, but if accompanied by expression of another oncogene, or if gene mutation or reduplication occurs, the cell may progress toward a malignant potential. Activation of 3 oncogenes (RET, RAS, BRAF) is seen in majority of papillary thyroid cancers. RET and TRK1 oncogenes lead to activation of tyrosine kinase and overexpression of its receptors. BRAF mutations activate the kinase, which stimulates the mitogen-activated protein kinase (MAPK) cascade. RAS mutations also stimulate the MAPK cascade, and are found in 30 % of thyroid neoplasms, including both papillary and follicular thyroid cancers. RET mutation are typical for familial medullary carcinomas. Anaplastic thyroid cancers (ATC) usually contain BRAF mutations and CTNNB1 (specific for ATC). Mutations of tumor suppressor p53 also play an important role in the development of ATC.

Thyroid neoplasms (adapted from WHO classification, 2017):

- Follicular adenoma
- Hyalinizing trabecular tumour
- Other encapsulated follicular patterned thyroid tumours
    - Follicular tumours of uncertain malignant potential
    - Well differentiated tumour of uncertain malignant potential

    - Noninvasive follicular thyroid neoplasm with papillary-like nuclear features
- Papillary thyroid carcinoma (and its variants: follicular, encapsulated, microcarcinoma, columnar cell variant, oncocytic)
- Follicular thyroid carcinoma
    - minimally invasive
    - encapsulated angioinvasive
    - widely invasive
- Hürthle (oncocytic) cell tumours (variants: adenoma, carcinoma)
- Poorly differentiated thyroid carcinoma
- Anaplastic thyroid carcinoma
- Squamous cell carcinoma
- Medullary thyroid carcinoma
- Mixed medullary and follicular thyroid carcinoma
- Mucoepidermoid carcinoma
- Sclerosing mucoepidermoid carcinoma with eosinophilia
- Mucinous carcinoma
- Ectopic thymoma
- Spindle epithelial tumour with thymus-like differentiation
- Intrathyroid thymic carcinoma
- Paraganglioma and mesenchymal / stromal tumours
- Hematolymphoid tumours (Langerhans cell histiocytosis, Rosai-Dorfman disease, follicular dendritic cell sarcoma, primary thyroid lymphoma)
- Germ cell tumours (teratomas: benign, immature, malignant)
- Secondary tumours

Clinical signs and symptoms.

Most frequently the tumor is discovered accidentally by the patient or physician as a lump in the neck or may be a random finding at ultrasound of the neck. It also may appear as a gradually enlarging, painful mass with associated symptoms of hoarseness, dysphagia or dysphonia, or there may be difficulty in breathing.

Occasionally, thyroid cancer presents with enlargement of the cervical lymph nodes, pulmonary symptoms from metastases, or a pathologic fracture of the spine or hip. Usually there are no symptoms of hyper-or hypothyroidism, but in very rare cases the tumor, can produce enough hormone to cause hyperthyroidism (usually metastatic follicular carcinoma).

Upon examination of the neck, carcinoma of the thyroid characteristically appears as an asymmetrical lump in the gland. If it is still located within the confines of the gland, it will move with the gland when the patient swallows and may be moveable within the gland. If it has invaded the trachea or neighboring structures, it may be fixed and this sign is very useful. Lymph nodes containing metastases may be found in the supraclavicular triangles, in the carotid chain, along the thyroid isthmus, and rarely in the axillary nodes. Although thyroid cancers are typically firm or hard, rapidly growing lesions, sometimes they might be soft or even fluctuant. When the tumor is poorly differentiated or anaplastic, the lesions may undergo necrosis and discharge through sinuses that developed on the skin surface of the neck.

Age at diagnosis has an important bearing on the patient's subsequent course. The adverse effect of age on the prognosis increases gradually with each decade. For practical assessment purposes, it is clear that patients diagnosed before age 45 have a much better prognosis than those detected later. Age is also directly related to the incidence of undifferentiated tumors and to overall mortality. Pregnancy does not seem to worsen the course of established or previously treated thyroid cancer. Overall, women have a better prognosis than men with cancer. Other characteristics of the

tumor, including extrathyroid extension, gross invasion of the tumor capsule, and increasing size also contain a bad prognosis.

Diagnosis. Most patients with thyroid carcinoma are recognized because of a positive or suspicious FNA done for the clinical or ultrasonographical discovery of a thyroid nodule, either single or in multinodular goiter. FNA and ultrasound are the key diagnostic methods in case of suspected thyroid cancer. TSH and free T4 are usually measured to verify metabolic status, and anti-TPO and TG antibodies may be useful in helping differentiate thyroiditis.

Thyroglobulin assay. Although TG assay has been suggested as an important marker for thyroid cancer, practice shows that elevated TG levels can be caused by adenoma, multinodular goiter, and other diseases; thus the determination is of little value before operation.

Chest Xray may be informative but is often omitted. In lesions which extend outside the thyroid, or have metastasis, ultrasound of the neck, *computer tomography* of the lungs, and *MRI* of the neck can provide useful information prior to surgery, and especially when following disease progress.

FNA cytology is currently the most precise and reliable method of diagnosis of thyroid neoplasms. FNA cytology of cervical nodes under ultrasound guidance is useful to detect local metastases.

Ultrasound. Typical features of ultrasonic scanning can suggest malignancy with quite good sensitivity. Microcalcifications, irregular margins, hypoechogeneicity, intranodular blood vessels and round shape are all in support of malignancy and may dictate the need for FNA. The ultrasound procedure has replaced other scanning procedures such as angiography, thermography, and fluorescent scanning. Thyroid elastosonography has been proposed recently as a very promising new tool to distinguish benign and malignant nodules.

*Isotope scans*have a limited role in initial diagnosis. Occasionally isotope scanning is useful in demonstration of hyperfunction in a nodule, lack of a lobe,

extension below the sternum, or other factors. Demonstrate of failure of the involved area to concentrate radioactive iodine used to be important, since malignant lesion are invariably cold at scan.

Positron emission tomography(PET) scan has been introduced recently and found informative for the imaging of metastatic disease devoid of 131-I uptake. 18-F fluorodeoxyglucose PET can localize tumor and determine tumor volume. Large deposits (>125ml) have a very adverse prognostic implication.

Papillary thyroid carcinoma accounts for 80 to 90% of all thyroid cancers. The female: male ratio is 3:1. It may be familial in up to 5% of patients. The typical age is 30 – 60 years. The tumor is often more aggressive in older patients. About two-thirds of papillary carcinomas contain follicular elements.

The tumor tends to remain localized in the thyroid gland and may exist for decades without killing the patient. Patients < 55 years with small tumors confined to the thyroid have an excellent prognosis.

In time, tumor spreads via lymphatic vessels to cervical or upper mediastinal nodes and may metastasize hematogenously to the lungs and bones. Lung metastases may appear as few nodules, or the lung fields may have a snowflake appearance throughout. These tumors can be well tolerated and may allow relatively normal physical activity for 10-30 years. At times, particularly in the follicular variant of papillary thyroid cancer, the pulmonary metastases are active in forming thyroid hormone, and may even function as the sole source of hormone supply after thyroidectomy. The metastases may progress gradually to obstructive and restrictive pulmonary disease. They also may develop arteriovenous shunts, with hypoxia or cyanosis.

Tumors > 4 cm or that are diffusely spreading require total or near-total thyroidectomy with postoperative radioiodine ablation of residual thyroid tissue with appropriately large doses of iodine-131 administered when the patient is hypothyroid

or after recombinant human thyroid-stimulating hormone injections. Treatment may be repeated after 6 to 12 months to ablate any remaining thyroid tissue.

TSH-suppressive doses of levothyroxine are given after treatment, and serum thyroglobulin levels are measured to help detect recurrent or persistent disease. Neck ultrasonography will detect recurrence in lymph nodes. About 20 to 30% of patients, mainly older patients, have recurrent or persistent disease.

Treatment for encapsulated tumors < 4 cm localized to one lobe is usually near-total thyroidectomy, although some experts recommend only lobectomy and isthmusectomy; surgery is almost always curative. Thyroid hormone in thyroid-stimulating hormone–suppressive doses is given to minimize chances of regrowth and cause regression of any microscopic remnants of papillary carcinoma. Active surveillance may be an alternative to surgery for papillary carcinomas < 1 to 1.5 cm with no evidence of lymph node or distant metastases.

Follicular thyroid carcinoma, including the Hurthle cell variant, accounts for about 10% of thyroid cancers and varies widely in different parts of the world. It is more common among older patients and in regions of iodine deficiency. The tumor is three times as common in women as in men. It is more malignant than papillary carcinoma, spreading hematogenously with distant metastases to lungs, bones or central nervous system. Bony metastases are usually osteolytic, rarely osteoblastic, and the alkaline phosphatase level is rarely elevated.

Treatment requires near-total thyroidectomy with postoperative radioiodine ablation of residual thyroid tissue as in treatment for papillary carcinoma. The tumor and metastases often retain an ability to accumulate and hold iodide, and are therefore sometimes susceptible to treatment with radioactive iodine. Indeed, some metastatic tumors synthesize thyroid hormone in normal or even excessive amounts. Radioactive iodine therapy, improves survival in these patients.

Thyroid-stimulating hormone-suppressive doses of l-thyroxine are given after treatment. Serum thyroglobulin measurements and neck ultrasonography should be done periodically to detect recurrent or persistent disease.

Medullary thyroid carcinoma constitutes about 4% of thyroid cancers and is composed of parafollicular cells (C cells) that produce calcitonin. It may be sporadic (usually unilateral); however, it is often familial, caused by a mutation of the RET proto-oncogene. The familial form may occur in isolation or as a component of multiple endocrine neoplasia (MEN) syndrome type 2A and MEN 2B.MEN 2A includes patients with medullary thyroid cancers, pheochromocytomas, and parathyroid hyperplasia or adenomas. MEN 2B includes medullary thyroid carcinoma, mucosal neuromas, pheochromocytomas, which are usually bilateral and often malignant, occasionally cafe-au-lait spots, and possibly Gardner's syndrome (mucocutaneous pigmented nevi and small intestinal polyps).

Familial medullary carcinoma is more aggressive than sporadic medullary carcinoma. The female to male ratio is almost equal.

Although calcitonin can lower serum calcium and phosphate levels, serum calcium is normal because the high level of calcitonin ultimately down-regulates its receptors. Characteristic amyloid deposits that stain with Congo red are also present.

Metastases spread via the lymphatic system to cervical and mediastinal nodes and sometimes to liver, lungs, and bones.

Patients typically present with an asymptomatic thyroid nodule. Gastrointestinal symptoms including diarrhea, constipation, and rarely megacolon occur in these patients and may occur before the thyroid tumor is detected. Many cases are now diagnosed during routine screening of affected relatives with MEN 2A or MEN 2B before a palpable tumor develops. Medullary carcinoma may have a various biochemical presentation when associated with ectopic production of other hormones or peptides (adrenocorticotropic hormone, vasoactive intestinal polypeptide, prostaglandins, kallikreins, serotonin).

The best test is measurement of serum calcitonin, which is greatly elevated. A challenge with calcium (15 mg/kg IV over 4 hours) provokes excessive secretion of calcitonin.

The thyroid primary tumor and the metastases may show a dense, homogenous, conglomerate calcification on X-ray film.

All patients with medullary thyroid carcinoma should have genetic testing; relatives of those with mutations should have genetic testing and measurement of basal and stimulated calcitonin levels. Every member of such family with either a thyroid mass or elevated calcitonin levels should have a thyroidectomy. If no thyroid nodule is detected and the serum calcitonin is normal according to the reference range for that specific age group, prophylactic thyroidectomy should be considered in order to remove the thyroid gland before the disease is initiated.

Total thyroidectomy is indicated for patients with confirmed medullary carcinoma even if bilateral involvement is not obvious. Lymph nodes are also dissected. If hyperparathyroidism is present, removal of hyperplastic or adenomatous parathyroids is required.

External radiation treatment and chemotherapy may provide palliation in patients with advanced disease.

Anaplastic thyroid carcinoma is an undifferentiated cancer that accounts for about 1% of thyroid cancers. It occurs mostly in older patients and slightly more often in women. The tumor is characterized by rapid, painful enlargement. Rapid enlargement of the thyroid may also suggest thyroid lymphoma, particularly if found in association with Hashimoto's thyroiditis.

No effective therapy exists, and the disease is generally fatal. About 80% of patients die within 1 year of diagnosis. In a few patients with smaller tumors, thyroidectomy followed by external beam radiation therapy has been curative. Chemotherapy is mainly experimental.

New potential therapies. Tyrosine kinase inhibitors are being explored as potential drugs to target pathways known to be active in thyroid cancer, including the RAS, BRAF, EGFR, VEGFR, and angiogenesis pathways. Positive results have been seen in trials using motesanib, sorafenib, and other agents. Very recently, one of this drugs, vandetanib, have been approved for the treatment of progressive, metastatic medullary thyroid carcinoma, based in clear evidence of beneficial effects in clinical trials.Therefore, target therapy might become the first line treatment of metastatic refractory thyroid cancer patients in the near future.

Review questions:

1. What is the most common type of thyroid cancer?
   A. Follicular
   B. Papillary
   C. Anaplastic
   D. Medullary
2. Which method of diagnosis of thyroid cancer is the most adequate?
   A. Palpation of the thyroid gland
   B. Isotope scanning
   C. FNA cytology under ultrasound guidance
   D. Ultrasound
3. What hormone is getting increased in the blood in case of medullary thyroid cancer?
   A. Triiodothyronine
   B. Thyroxine
   C. Calcitonin
   D. TSH
4. What type of thyroid cancer may be accompanied with hyperthyroidism?
   A. Follicular

B. Papillary

C. Anaplastic

D. Medullary

5. What type of thyroid cancer is characterized by active absorption of ^{131}I?

A. Papillary

B. Anaplastic

C. Medullary

D. Follicular

6. What type of thyroid cancer is the most susceptible to treatment with radioactive iodine?

A. Papillary

B. Follicular

C. Anaplastic

D. Medullary

7. What type of thyroid cancer can occur as a component of multiple endocrine neoplasia syndrome?

A. Papillary

B. Follicular

C. Anaplastic

D. Medullary

8. The most aggressive type of thyroid cancer is:

A. Papillary

B. Follicular

C. Anaplastic

D. Medullary

9. What is the main method of treatment for well-differentiated thyroid cancers?

A. Surgery

B. Radioactive iodine

C. L-thyroxine

D. Chemotherapy

10. What are the common sites for thyroid cancer metastases?

A. Lymph nodes

B. Lungs

C. Bones

D. All of theabove

Case-based questions on thyroid diseases.

1. A 45-year-old patient has had a 3-week history of upper respiratory tract infection followed by general malaise. She now is complaining of pain in her neck and sore throat. She denies palpitations, nervousness, or diaphoresis. Her thyroid is diffusely enlarged and tender. Her erythrocyte sedimentation rate (ESR) and T4 levels are elevated. What is the first-line treatment for this patient?

A. NSAIDs and rest
B. Corticosteroids
C. Levothyroxine
D. Atenolol

2. A 28-year-old woman has had difficulty concentrating at work for the past month. She is constantly getting up and walking around to visit co-workers. She complains that the work area is too hot. She seems nervous and often spills her coffee. She has been eating more but has lost 5 kg in the past 2 months. On physical examination her temperature is 37.5°C, pulse 101/minute, respiratory rate 22/minute, and blood pressure 145/85 mm Hg. Which of the following laboratory findings is most likely to be present in this woman?

A. Decreased plasma insulin
B. Decreased TSH
C. Increased ACTH
D. Increased calcitonin

3. A 40-year-old woman has noted enlargement of her anterior neck region over the past 8 months. On physical examination her vital signs include T 36.8°C, P 64/minute, RR 16/minute, and BP 155/105 mm Hg. There is diffuse, symmetrical thyroid enlargement without tenderness. A chest radiograph is normal. Fine needle

aspiration of the thyroid yields cells consistent with a neoplasm. Laboratory studies show that she is euthyroid, but her serum ionized calcium is elevated. She is taken to surgery and frozen sections of several thyroid masses show a malignant neoplasm composed of polygonal cells in nests. A thyroidectomy is performed. Immunostaining for calcitonin of the permanent sections is positive, and the neoplasm has an amyloid stroma with Congo red staining. Which of the following neoplasms is she most likely to have?

A. Anaplastic carcinoma
B. Medullary carcinoma
C. Papillary thyroid carcinoma
D. Follicular carcinoma

4. A 37-year-old man experiences abdominal pain, nausea, and constipation for the past 3 days. On physical examination he has no palpable abdominal masses and bowel sounds are present. His lungs are clear to auscultation. He has a heart rate of 80/min with an irregular rhythm. An electrocardiogram demonstrates a shortened QT(corrected) interval and a prolonged PR interval. He has a stool positive for occult blood. Upper GI endoscopy reveals multiple 1 cm diameter shallow ulcerations of the gastric antrum. Which of the following laboratory test findings is most likely to be present in this man?

A. Thyroid peroxidase antibody of 4 IU/mL
B. Serum calcium of 12.4 mg/dL
C. Blood glucose of 225 mg/dL
D. Total serum thyroxine of 21 ng/mL
E. Plasma cortisol of 45 microgm/dL at 8 am

5. A 40-year-old female complains of a sore throat, difficulty swallowing, and intermittent fevers for about a week. She had an upper respiratory infection just a few

weeks ago. She has no significant past medical history. A physical exam reveals an enlarged and tender thyroid. Her oropharynx is clear, and she has no cervical lymphadenopathy. Laboratory evaluation shows a WBC count of 13,000 cells/microliter with a normal differential, thyroid stimulating hormone (TSH) 19 microIU/mL, and erythrocyte sedimentation rate (ESR) 45 mm/hr. What is the most probable diagnosis?

A. Hashimoto thyroiditis
B. Postpartum thyroiditis
C. De Quervain (subacute) thyroiditis
D. Suppurative thyroiditis

6. A 58-year-old man with a history of diabetes mellitus has noted the presence of bone pain, especially of his hands, for the past 6 months. On physical examination there is no swelling or redness of his hands, no joint deformity, but the range of motion is slightly decreased. Laboratory studies show sodium 139 mmol/L, potassium 4.0 mmol/L, chloride 98 mmol/L, C02 22 mmol/L, glucose 153 mg/dL, creatinine 7.8 mg/dL, calcium 7.8 mg/dL, phosphorus 5.7 mg/dL, total protein 6.2 g/dL, and albumin 4.0 g/dL. Which of the following conditions is this man most likely to have?

A. Adrenal adenoma
B. Medullary thyroid carcinoma
C. Extra-adrenal pheochromocytoma
D. Parathyroid hyperplasia

7. A 49-year-old woman has had increasing cold intolerance, weight gain of 4 kg, and sluggishness over the past two years. A physical examination reveals dry, coarse skin and alopecia of the scalp. Her thyroid is not palpably enlarged. Her serum TSH is 11.7 mU/L with thyroxine of 2.1 micrograms/dL. A year ago, anti-

thyroglobulin and anti-microsomal autoantibodies were detected at high titer. Which of the following thyroid diseases is she most likely to have?

A. DeQuervain disease
B. Papillary carcinoma
C. Hashimoto thyroiditis
D. Multinodular goiter

8. An 35-year-old woman has had insomnia for the past 4 months, as well as episodes of diarrhea with up to 4 loose stools per day. On physical examination, she exhibits bilateral proptosis. Her outstretched hands have a fine tremor. On palpation of her neck, the thyroid gland does not appear to be enlarged and no masses are palpable. Laboratory studies show a serum TSH of 8.8 microU/mL in association with a serum total thyroxine of 15.1 microgram/dL. Which of the following is the most likely diagnosis?

A. Graves disease
B. Pituitary adenoma
C. Chronic thyroiditis
D. Prior thyroidectomy

9. A 25-year-old woman has had a 7 kg weight loss over the past 6 months without dieting or trying to lose weight. On physical examination she appears anxious and worried. Her hands are warm and tremulous. Vital signs show her temperature to be 37.4°C, pulse 105/minute, respirations 23/minute, and blood pressure 135/75 mm Hg. Serum laboratory data include glucose 78 mg/dL and creatinine 0.8 mg/dL. Which of the following additional laboratory test findings is most likely to be present in this woman?

A. Plasma cortisol of 40 microgm/dL at 8 am
B. Serum antinuclear antibody of 1:256

C. Urinary free catecholamines of 500 microgm/24 hr

D. Serum total thyroxine of 14 microgm/dL

10. A 47-year-old woman feels a 'lump' in her neck that she didn't notice 5 months before. Her physician palpates a firm nodule about 2 cm in size to the left of midline in the region of the thyroid gland. By scintigraphic scanning this nodule appears 'cold' with normal activity in the surrounding normally sized thyroid gland. Which of the following is the most likely diagnosis?

A. Papillary carcinoma

B. Follicular adenoma

C. Thyroglossal duct cyst

D. Toxic nodular goiter

11. A 40-year-old woman notes increasing enlargement and discomfort in her neck over the past week. The nurse practitioner palpates diffuse, symmetrical enlargement with tenderness in the region of the thyroid gland. Thyroid function tests show serum TSH of 0.8 mU/L and thyroxine of 11.9 micrograms/dL. She is referred to an endocrinologist, but the next available appointment is in 8 weeks. When examined by the endocrinologist her thyroid is no longer palpable and there is no pain. Repeat thyroid function tests reveal a serum TSH of 3.8 mU/L and thyroxine of 5.7 micrograms/dL. Which of the following thyroid diseases is most likely to produce these findings?

A. Nodular goiter

B. DeQuervain thyroiditis

C. Hashimoto thyroiditis

D. Graves disease

12. A 53-year-old woman has pain in her neck for the past month. On physical examination her vital signs include T 37°C, P 77/minute, RR 16/minute, and BP 130/80 mm Hg. There is an irregular firm mass palpable in her left neck. A CT scan shows an infiltrative mass involving the left lobe of the thyroid and extending into adjacent soft tissues. Laboratory studies show TSH 2.9 mU/L, total serum thyroxine 8.6 microgm/dL, calcium 8.7 mg/dL, and phosphorus 2.8 mg/dL. A fine needle aspiration biopsy of the mass shows malignant spindle-shaped cells present that demonstrate a p53 mutation immunohistochemically. Which of the following neoplasms is this woman most likely to have?

A. Papillary carcinoma
B. Follicular adenoma
C. Anaplastic carcinoma
D. Medullary carcinoma

13. A 40-year-old woman has noted painless swelling of her neck for the past 3 weeks. On physical examination there is diffuse enlargement of her thyroid. Laboratory studies show an increased titer of anti-thyroid peroxidase and anti-thyroglobulin antibodies. Within a month, the swelling has diminished. Which of the following complications is she most likely to develop?

A. Amyloidosis
B. Hypothyroidism
C. Papillary carcinoma
D. Riedel thyroiditis

14. A 38-year-old woman has had a feeling of fullness in her neck for the past year. She is otherwise asymptomatic. Her physician's assistant palpates a symmetrically enlarged but nontender thyroid gland. She has no difficulty swallowing. There is no palpable lymphadenopathy. She is afebrile. Her serum TSH

is 3.5 mU/L with total thyroxine of 8.2 micrograms/dL. Thyroid peroxidase antibody is not detected. Two years later, her thyroid has not appreciably changed in size. Which of the following conditions is she most likely to have?

A. Graves disease
B. Nodular goiter
C. Hashimoto thyroiditis
D. Follicular adenoma

15. A 30-year-old woman from Barcelona has noted enlargement of her neck over the past 4 months. On physical examination, she has a diffusely enlarged thyroid that is not painful to palpation. Her TSH level is 0.2 mU/L. A subtotal thyroidectomy is performed and histologically the tissue shows follicles with papillary infoldings lined by tall columnar cells. Which of the following is the most likely diagnosis?

A. Papillary carcinoma
B. Multinodular goiter
C. Hashimoto thyroiditis
D. Graves disease

16. A 2-year-old child living in Odessa is small for its age and exhibits profound intellectual disability. On physical examination he has dry, coarse skin. Which of the following pathologic features involving the thyroid gland is this child most likely to have?

A. Diffuse hyperplasia
B. Granulomatous inflammation
C. Metastatic carcinoma
D. Marked atrophy

17. A 35-year-old woman has increasing fullness in her neck for the past 5 months since delivery of her last infant. On physical examination her thyroid gland is diffusely enlarged but not painful to palpation. Laboratory studies show an anti-thyroglobulin titer of 1:256 and an anti-thyroid peroxidase titer of 1:512. Her TSH and thyroxine are normal. Which of the following is the most likely diagnosis?

A. Diffuse goiter
B. Subacute granulomatous thyroiditis
C. Subacute lymphocytic thyroiditis
D. Adenovirus infection

18. A 39-year-old woman has noted discomfort with fullness to her neck over the past year. On physical examination she is afebrile and normotensive. There is irregular enlargement of her thyroid gland, but no tenderness on palpation. A scintigraphic scan shows normal uptake except for increased uptake in a 1 cm area in the left lower lobe. Her anti-thyroid peroxidase antibody is negative. Which of the following complications is she most likely to develop?

A. Thyrotoxicosis
B. Subacute thyroiditis
C. Papillary carcinoma
D. Hypothyroidism

19. A 14-year-old boy has felt a 'bump' in his neck for the past year. On physical examination just anterior to the trachea in the midline is a palpable non-tender 2 cm mass. A fine needle aspirate of the mass yields only clear, mucoid fluid. Which of the following is the most likely diagnosis?

A. Thyroglossal duct cyst
B. Follicular adenoma
C. Nodule of a multinodular goiter
D. Lymph node metastasis of follicular carcinoma

20. A 47-year-old woman has felt a 'lump' in her neck for the past 2 months. On physical examination there is a firm nodule in the right lobe of her thyroid. Following fine needle aspiration and cytologic diagnosis of a neoplasm, a thyroidectomy is performed. Grossly, there is a 3 cm mass in the right lower pole that on sectioning is cystic and has papillary excrescences. Which of the following microscopic pathologic findings is most typical for this lesion?

A. Giant cells
B. Amyloid stroma
C. Small thyroid follicles
D. Clear nuclear chromatin

Correct answers for review questions.

	Question 1	2	3	4	5	6	7	8	9	10
Chapter1	D	B	C	C	D	A	D	B	C	A
2	D	C	A	A	C	D	B	B	A	A
3	A	B	C	D	B	B	A	C	D	C
4	C	A	D	D	C	D	B	A	C	B
5	B	C	C	A	D	B	D	C	A	D

Correct answers for case-based questions on thyroid diseases.

1. (A) Patient's clinical and lab data are suggestive of De Quervain (subacute) thyroiditis. The first line treatment includes nonsteroid anti-inflammatory drugs and rest in case of neck pain and sore throat while thyrotoxicosis signs is absent

2. (D) She has Graves disease with hyperthyroidism. There are both thyroid-stimulating immunoglobulins (TSI) and thyroid growth-stimulating immunoglobulins (TGI) in Graves disease. The amount of thyroid hormone production goes up, suppressing TSH secretion from the pituitary. The diffusely enlarged thyroid gland is double to triple in size, which is still difficult to appreciate on physical examination.

3. (B) She has MEN IIa, with medullary thyroid carcinomas (often multiple when familial), parathyroid hyperplasia, and pheochromocytoma.

4. (B) He most likely has a parathyroid adenoma secreting excessive parathormone to increase serum calcium and decrease serum phosphorus. The hypercalcemia leads to increased gastrin production and peptic ulcer disease. Hypercalcemia produces cardiac arrhythmias (or asystole).

5. (C) The history of recent upper respiratory infection, enlarged and tender thyroid on palpation, increased TSH due to the development of hypothyroidism, and inflammatory changes of CBC suggest the presence of De Quervain (subacute) thyroiditis.

6. (D)He has secondary hyperparathyroidism from chronic renal failure. Renal failure with retention of phosphorus drives the calcium down and parathormone secretion up, leading to osteitis fibrosa cystica and bone pain.

7. (C)Hashimoto thyroiditis is the most common cause for hypothyroidism in adults. Though the thyroid may initially have been painlessly enlarged, over time the inflammation leads to atrophy of the thyroid with hypothyroidism. Anti-thyroid autoantibodies are helpful in establishing the diagnosis.

8. (B) This combination of tests suggests that there is excess TSH coming from the pituitary, but there is no feedback inhibition, because the thyroxine is also high. This suggests a pituitary adenoma is present. Such a TSH secreting pituitary adenoma is an uncommon cause for hyperthyroidism.

9. (D)She is manifesting the signs and symptoms of hyperthyroidism and probably has Graves disease.

10. (B)The majority of 'cold' thyroid nodules are benign and many are adenomas. Follicular neoplasms are difficult to definitively classify, and even some that appear histologically benign may eventually act in a more aggressive manner.

11. (B)Granulomatous thyroiditis tends to be a self-limited disease that runs a course over weeks. Patients may initially be hyperthyroid, then hypothyroid, then euthyroid. Prior viral infection is implicated in some cases.

12. (C)Anaplastic carcinoma of the thyroid is a highly aggressive, infiltrative mass lesion with a poor prognosis. Fortunately, it is rare.

13. (B) Hypothyroidism can occur years later in the course of Hashimoto thyroiditis, even though there may initially be transient hyperthyroidism. Eventually the inflammation leads to loss of thyroid follicles. This is the most common cause for hypothyroidism in adults.

14. (B) The most common cause for thyroid enlargement is a simple, nodular goiter. Most patients are euthyroid with this condition. Places far away from a seacoast (a source for iodine) are where endemic goiter used to be seen. Use of iodized salt eliminated the problem.

15. (D)Diffuse hyperplasia with active thyroid epithelial cells is typical for Graves disease. The TSH is low from negative feedback from the increased thyroid hormone production.

16. (D) The child is not living in a region of endemic goiter. His thyroid problem is probably a developmental failure of thyroid gland formation. congenital hypothyroidism, though rare, is one of the diseases screened for at birth, because when recognized it can easily be treated with replacement thyroid hormone. However, the health care system needs to function effectively to diagnose and treat preventable diseases.

17. (C) Some postpartum women have thyroid autoantibodies. Microscopically, extensive lymphoid infiltrates also suggest autoimmunity as an etiology for thyroid disease. Early in the course of subacute lymphocytic thyroiditis, the thyroid may be enlarged from extensive inflammation. Hyperthyroidism may be transient, and most persons are euthyroid. A small number of affected persons develop hypothyroidism.

18. (A) Multinodular goiter is the result of long-standing simple goiter. A toxic multinodular goiter (Plummer syndrome) occurs in less than half of patients with multinodular goiter. A hyperfunctioning nodule is the source for increased thyroid hormone.

19. (A) This vestigial midline remnant of thyroid development may become manifest at any age and is the most common clinically significant congenital thyroid anomaly. A thyroglossal duct (tract) cyst can be easily excised. In embryologic development, thyroid anlage begin at the foramen cecum of the tongue and migrated downward, past the hyoid bone, to the location of thyroid gland. Remnants may be present along that route.

20. (D) The histologic finding of cell nuclear clearing is the hallmark of a papillary carcinoma, and lymph node is the first site for metastasis.

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для студентів та лікарів-інтернів

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