Thyroid disorders (part 2)

Lorina Vudu

- Hypothyroidism is a complex syndrome characterized by absence or inefficacy of thyroid hormone action upon various metabolisms, organs and systems. The severe form of H. is also called "myxoedema“. This denomination is somehow insufficient, taking into account that myxoedema represents only the cutaneous manifestation of H.

Classification

- It usually is a **primary** process in which the thyroid gland is unable to produce sufficient amounts of thyroid hormone.
- H. can also be **secondary**—that is, the thyroid gland itself is normal, but it receives insufficient stimulation because of low secretion of thyrotropin [TSH] from the pituitary gland.
- In **tertiary** H., inadequate secretion of thyrotropin-releasing hormone (TRH) from the hypothalamus leads to insufficient release of TSH, which in turn causes inadequate thyroid stimulation.

Primary H.

- **<u>At birth:</u>**

- Thyroid gland agenesy;
- Thyroid gland ectopy;
- Hormonosynthesis disturbances;
- Severe iodine deficiency;
- I131 administration during pregnancy;
- Administration antithyroid drugs during pregnancy

- **<u>Acquired postnatally:</u>**

- Autoimmune thyroiditis;
- Surgical thyroidectomy;
- Thyroid gland destruction by I131;
- Therapeutic thyroid gland blockage

Secondary H.

- Pituitary disease affecting TSH secretion and producing (“the 9 I‘s: Infarction, Infiltrative, Injury, Invasive, Immunologic, Iatrogenic, Infectios, Idiopathic, Isolated")

Tertiary H.

- Hypothalamic involvement producing TRH deficiency: tumors, infections, etc.
- Incidence: clinically manifest H.: 1-6% of the general population.
- Primary thyroid disease accounts for over 95 percent of cases of hypothyroidism.
- Sex ratio: primary H.: 7/1 for females.

  secondary: 1/1

- The symptoms and signs of hypothyroidism vary in relation to the magnitude of the thyroid hormone deficiency and the acuteness with which the deficiency develops.
- the most frequent presenting symptoms of hypothyroidism are nonspecific.

Clinical manifestations

- reflect one of two changes induced by lack of thyroid hormone
- - A generalized slowing of metabolic processes. This can lead to abnormalities such as fatigue, slow movement and slow speech, cold intolerance, constipation, weight gain (but not morbid obesity), delayed relaxation of deep tendon reflexes, and bradycardia.
- - Accumulation of matrix glycosaminoglycans in the interstitial spaces of many tissues. This can lead to coarse hair and skin, puffy facies, enlargement of the tongue, and hoarseness. These changes are often more easily recognized in young patients, and they may be attributed to aging in older patients.

Major symptoms and signs of hypothyroidism

Mechanism	Symptoms	Signs
Slowing of metabolic processes	Fatigue and weakness Cold intolerance Dyspnea on exertion Weight gain Cognitive dysfunction Mental retardation (infantile onset) Constipation Growth failure	Slow movement and slow speech Delayed relaxation of tendon reflexes Bradycardia Carotenemia
Accumulation of matrix substances	Dry skin Hoarseness Edema	Coarse skin Puffy facies and loss of eyebrows Periorbital edema Enlargement of the tongue
Other	Decreased hearing Myalgia and paresthesia Depression Menorrhagia Arthralgia Pubertal delay	Diastolic hypertension Pleural and pericardial effusions Ascites Galactorrhea

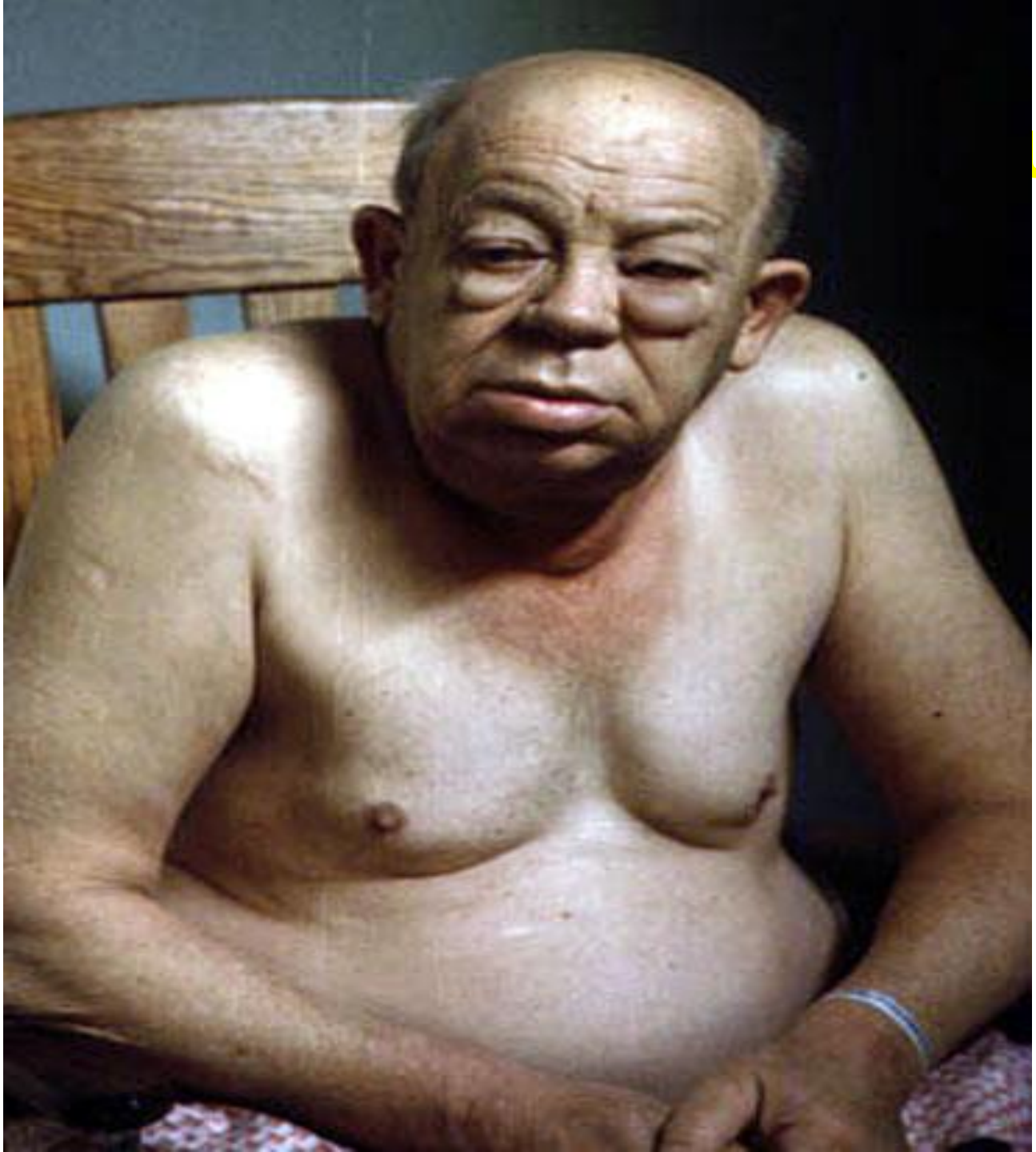
Skin

- Sweating is decreased because of decreases in calorigenesis and acinar gland secretion.
- Skin discoloration may occur. A yellowish tinge may be present if the patient has carotenemia, while hyperpigmentation may be seen when primary hypothyroidism is associated with primary adrenal failure.
- Hair may be coarse, hair loss is common, and the nails become brittle.
- Nonpitting edema (myxedema) occurs in severe hypothyroidism and may be generalized. It results from infiltration of the skin with glycosaminoglycans with associated water retention.
- Vitiligo and alopecia areata may be present in patients with hypothyroidism.

Eyes

Periorbital edema often presents as a manifestation of generalized nonpitting edema.

In addition, Graves' ophthalmopathy may persist when hypothyroidism develops after treatment of Graves‘ hyperthyroidism. Thus, periorbital edema may also be a manifestation of ophthalmopathy, in which case the patient may also have variable degrees of stare, protrusion of the eyes, and extraocular muscle weakness.



Hematologic

Patients with hypothyroidism appear to be at increased risk of bleeding due to a hypothyroidism-associated hypocoagulable state, caused by an acquired von Willebrand's syndrome typeI.

Anemia

Patients with hypothyroidism have a decrease in red blood cell mass and a normochromic, normocytic hypoproliferative anemia. Pernicious anemia occurs in 10 percent of patients with hypothyroidism caused by chronic autoimmune thyroiditis. Such patients present with a macrocytic anemia with marrow megaloblastosis. Women in the childbearing years may develop iron deficiency anemia, secondary to menorrhagia. In patients with iron deficiency anemia and hypothyroidism, combined therapy with levothyroxine and oral iron supplements results in correction of the anemia, which may be refractory to treatment with iron alone.

Cardiovascular system

- The systemic hypometabolism that is associated with hypothyroidism results in a decrease in cardiac output that is mediated by reductions in heart rate and contractility. Thyroid hormone regulation of genes coding for specific myocardial enzymes involved in myocardial contractility and relaxation is responsible for the decrease in contractility.
- Reduced cardiac output probably contributes to decreased exercise capacity and shortness of breath during exercise, two common complaints in patients with hypothyroidism. However, symptoms and signs of congestive heart failure are usually absent in patients who have no other cardiac disease. By contrast, heart failure or angina may worsen when hypothyroidism develops in patients with heart disease. In such patients, thyroxine (T4) replacement should be administered cautiously, beginning with a low initial dose (eg, 25 mcg) and then increasing in small increments every one or two months.

- Other abnormalities contributing to cardiovascular disease that may occur in hypothyroid patients are:
- Pericardial effusion, which only rarely compromises ventricular function.
- Hypertension, because of an increase in peripheral vascular resistance. In normotensive patients, blood pressure increases are small (eg, maximal blood pressure less than 150/100 mmHg). The blood pressure of patients with established hypertension, however, may increase further with the development of hypothyroidism.
- Hypercholesterolemia, which is caused by a decrease in the rate of cholesterol metabolism.
- Hyperhomocystemia.

Respiratory system

- Fatigue, shortness of breath on exertion, rhinitis, and decreased exercise capacity may result from impaired respiratory function, as well as cardiovascular disease. Hypoventilation occurs because of respiratory muscle weakness and reduced pulmonary responses to hypoxia and hypercapnia. Although respiratory muscle function is restored by T4 replacement, normalization of gas exchange may not occur, particularly in obese patients.
- Sleep apnea occurs in some patients with hypothyroidism, mostly as a result of macroglossia. Treatment of the hypothyroidism will usually reverse the sleep apnea, but some patients require treatment with continuous positive airway pressure (CPAP)
- The prevalence of hypothyroidism is high among patients with idiopathic pulmonary arterial hypertension, although hypothyroidism is not currently believed to be a risk factor for the condition. The basis of the observed association of the two disorders is unclear.

Gastrointestinal disorders

- Decreased gut motility results in constipation, one of the most common complaints of patients with hypothyroidism. When euthyroid patients who already have constipation become hypothyroid, their constipation worsens. In occasional patients, marked ileus may be confused with intestinal obstruction.

Other gastrointestinal problems that can occur in hypothyroidism are:

- Decreased taste sensation.

- Gastric atrophy due to the presence of antiparietal cell antibodies. Pernicious anemia occurs in 10 percent of patients with hypothyroidism caused by chronic autoimmune thyroiditis.

- Celiac disease is four times more common in hypothyroid patients compared with the general population.

- A modest weight gain due to decreased metabolic rate and accumulation of fluid (nonpitting edema) that is rich in glycosaminoglycans is a frequent finding. However, marked obesity is not characteristic of hypothyroidism.
- Ascites is a rare finding.

Reproductive abnormalities

- Women with hypothyroidism may have either oligo- or amenorrhea or hypermenorrhea -menorrhagia.
- These menstrual changes result in decreased fertility. If pregnancy does occur, there is an increased likelihood for early abortion. Hyperprolactinemia may occur, and is occasionally sufficiently severe to cause amenorrhea or galactorrhea.
- Decreased libido, erectile dysfunction, and delayed ejaculation are found in hypothyroid men. In one report, sperm morphology was abnormal in 64 percent of hypothyroid men before treatment and 24 percent after T4 therapy.

Neurological dysfunction

- The neurologic manifestations of hypothyroidism are both common and protean, affecting both the central and peripheral nervous system. Neurologic manifestations of hypothyroidism can cause significant disability.

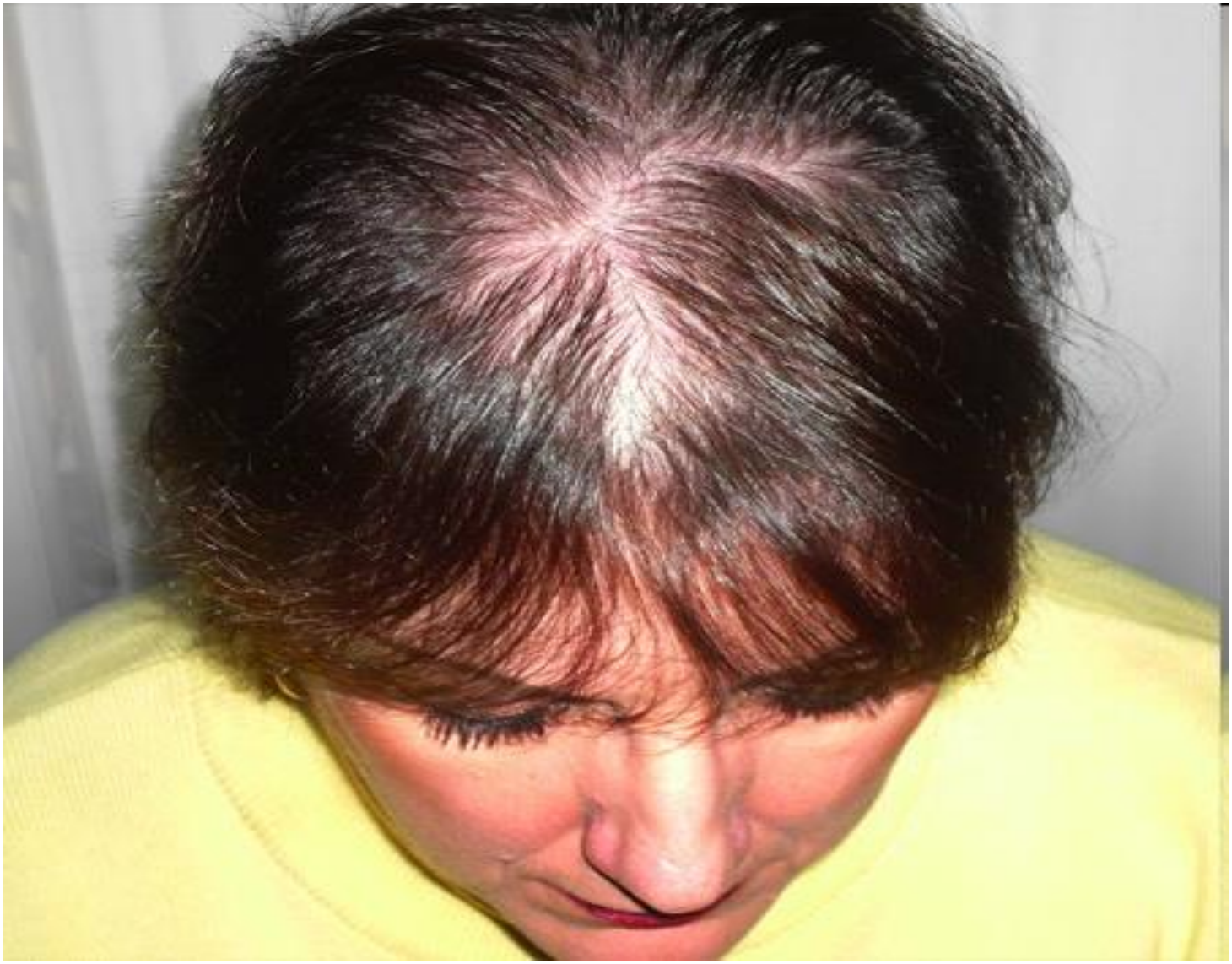
Slowing of intellectual function, “memory“ gaps, depressive syndromes, paresthesy of extremities, mucoid infiltration of muscle fibres, carpal tunnel syndrome. Most of these complications are partially or fully responsive to thyroid replacement.

Muscular system

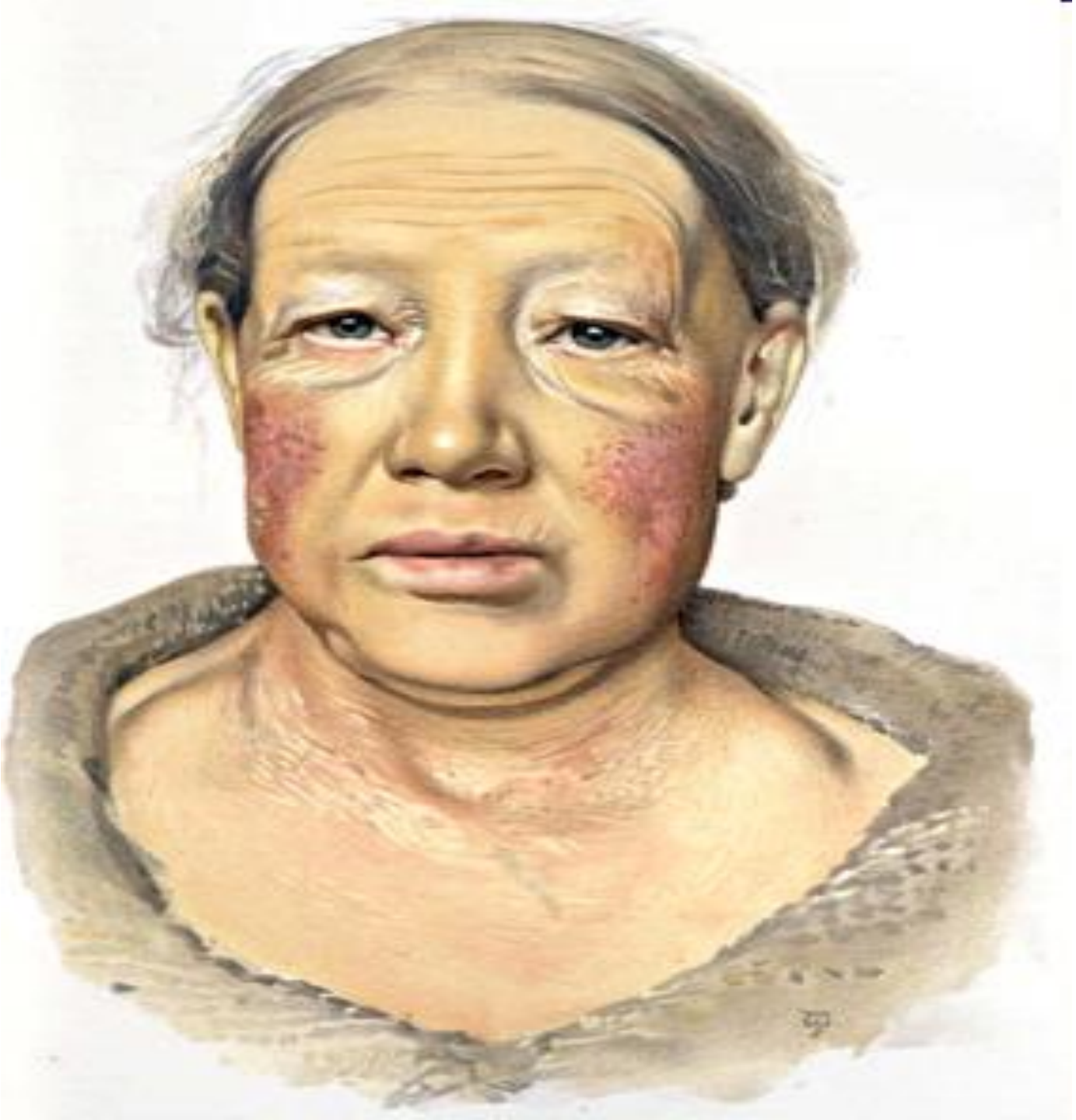
- Muscle atrophy, mucoid infiltration of muscles with pseudoathletic aspect, slow muscular contraction and relaxation (with prolonged Achillean reflex), painful muscular cramps.
- Physical examination findings may include goiter (particularly in patients with iodine deficiency or goitrous chronic autoimmune thyroiditis [Hashimoto's thyroiditis]), bradycardia, hypertension, and a delayed relaxation phase of the deep tendon reflexes.

Physical signs of hypothyroidism include the following:

- Weight gain
- Slowed speech and movements
- Dry skin
- Jaundice
- Pallor
- Coarse, brittle, straw-like hair
- Loss of scalp hair, axillary hair, pubic hair, or a combination
- Dull facial expression
- Coarse facial features
- Periorbital puffiness

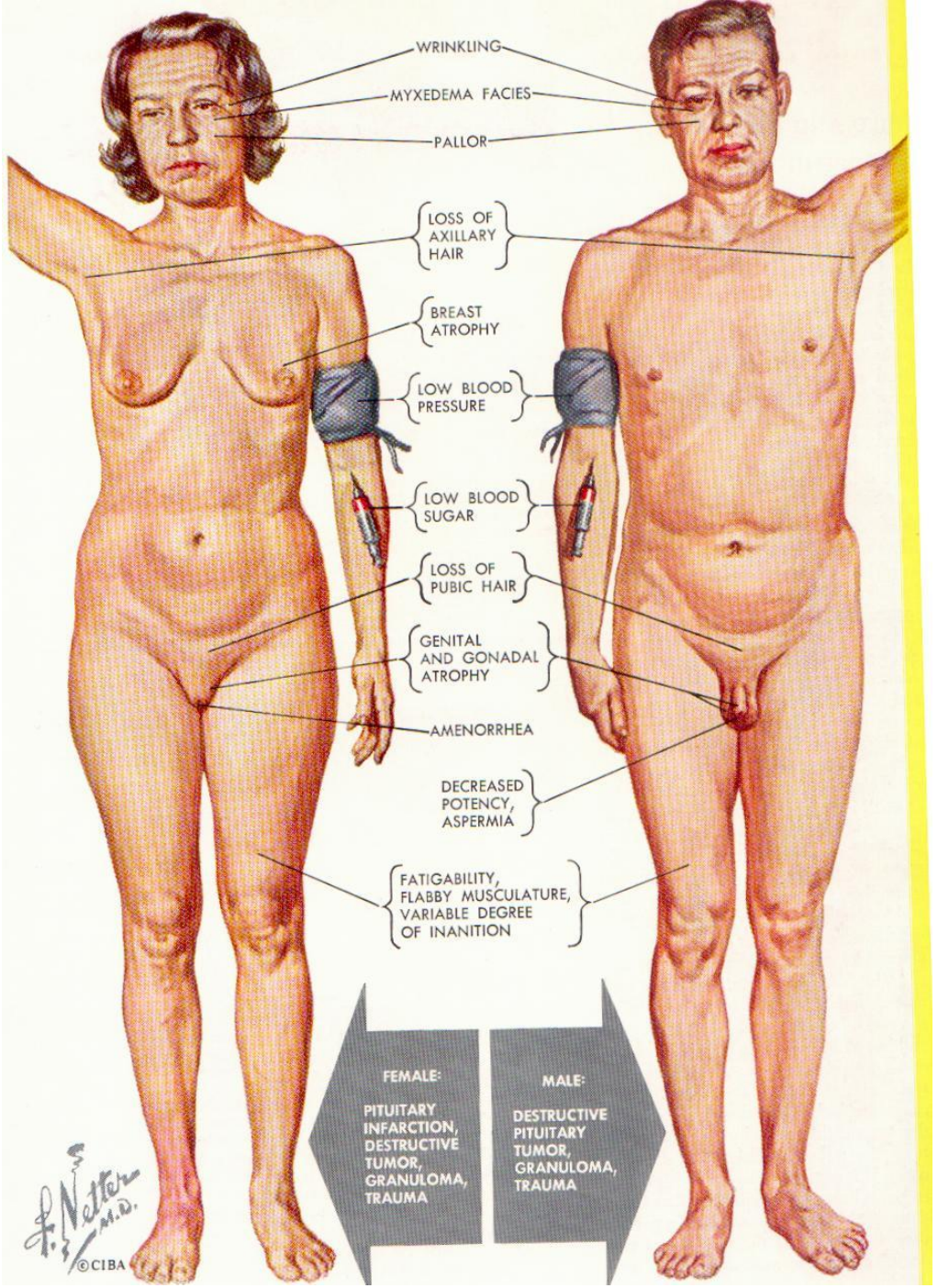


- Macroglossia
- Hoarseness
- Decreased systolic blood pressure and increased diastolic blood pressure
- Pericardial effusion
- Abdominal distention, ascites (uncommon)
- Hypothermia (only in severe hypothyroid states)
- Nonpitting edema (myxedema)
- Pitting edema of lower extremities
- Hyporeflexia with delayed relaxation, ataxia, or both



- The clinical manifestations of central hypothyroidism are similar to those of primary hypothyroidism. When hypothyroidism is caused by hypothalamic-pituitary disease, the manifestations of associated endocrine deficiencies such as hypogonadism and adrenal insufficiency may mask the manifestations of hypothyroidism.

Insuficienţa hipofizară



DIAGNOSIS

- Because of the lack of specificity of the typical clinical manifestations, the diagnosis of hypothyroidism is based primarily upon laboratory testing.
- The serum TSH should be the initial test.
- Primary hypothyroidism is characterized by a high serum TSH concentration and a low serum free T4 concentration. Patients with a high serum TSH concentration and a normal serum free T4 concentration may have subclinical hypothyroidism.
- Central hypothyroidism is characterized by a low serum T4 concentration and a serum TSH concentration that is not appropriately elevated. In this setting, differentiation must be made between pituitary (secondary hypothyroidism) and hypothalamic (tertiary hypothyroidism) disorders.

- Substantial hyperlipidemia or a change in lipid pattern, which occurs with increased frequency in hypothyroidism.
- Hyponatremia, often resulting from inappropriate production of antidiuretic hormone, which is another laboratory manifestation of hypothyroidism.
- Serum concentrations of thyroid peroxidase autoantibodies are elevated in more than 90 percent of patients with hypothyroidism due to chronic autoimmune hypothyroidism (Hashimoto's thyroiditis).
- High serum muscle enzyme concentrations.
- Macrocytic anemia.
- Pericardial or pleural effusions

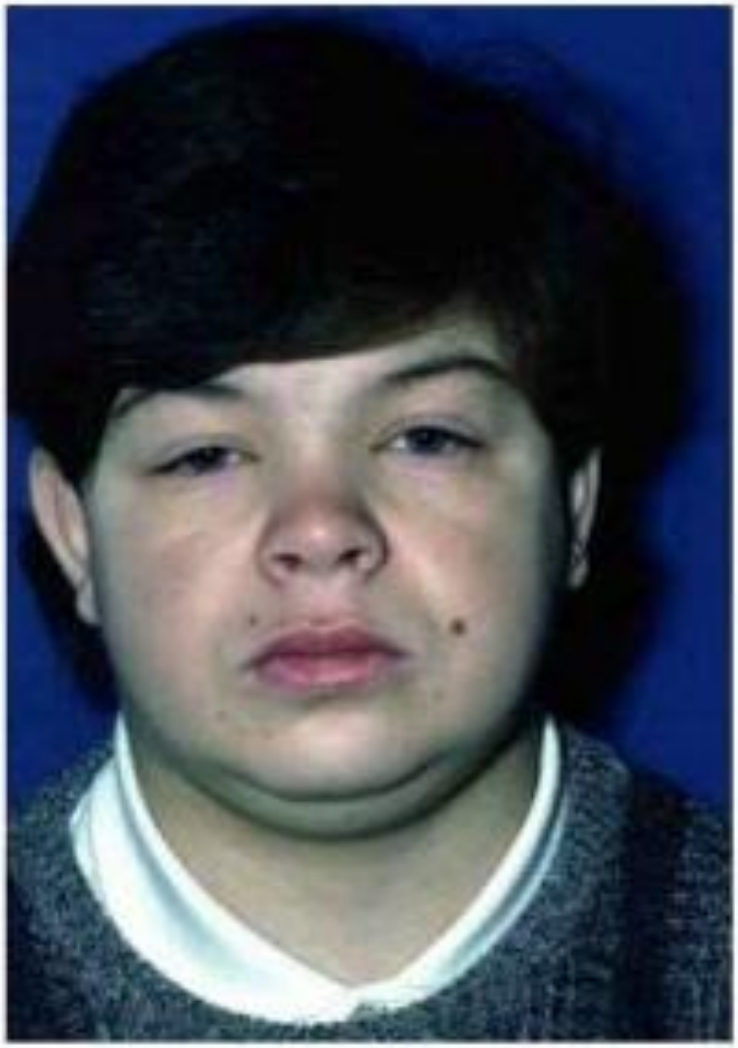
Treatment of hypothyroidism

- — In most patients, hypothyroidism is a permanent condition requiring lifelong treatment. Therapy consists of thyroid hormone replacement unless the hypothyroidism is transient (as after painless thyroiditis or subacute thyroiditis) or reversible (due to a drug that can be discontinued).
- The goal of therapy is restoration of the euthyroid state, which can be readily accomplished in almost all patients by oral administration of synthetic thyroxine (T4). Appropriate treatment reverses all the clinical manifestations of hypothyroidism.

The treatment of choice for correction of hypothyroidism is synthetic thyroxine (T4). Approximately 80 percent of a dose of T4 is absorbed and, because the plasma half-life of T4 is long (seven days), once-daily treatment results in nearly constant serum T4 and triiodothyronine (T3) concentrations when a steady state is reached.

The average replacement dose of T4 in adults is approximately 1.6 mcg/kg body weight per day (112 mcg/day in a 70-kg adult), but the range of required doses is wide, varying from 50 to ≥200 mcg/day. T4 requirements correlate better with lean body mass than total body weight. The necessary dose per kg body weight is higher in infants and children.

Tratamentul hipotiroidismului



- should be taken on an empty stomach, ideally an hour before breakfast, but few patients are able to wait a full hour.
- The initial dose can be the full anticipated dose (1.6 mcg/kg/day) in young, healthy patients, but older patients should be started on a lower dose (25 to 50 mcg daily).
- after initiation of T4 therapy, the patient should be reevaluated and serum TSH measured in six weeks. If the TSH remains above the normal reference range, the dose of T4 can be increased by 12 to 25 mcg/day. The patient will require a repeat TSH measurement in six weeks.

- The efficacy of T4 therapy in patients with central hypothyroidism must be monitored clinically and by measurements of serum T4; measurements of serum TSH are of no value.

Thyroiditis

- The term thyroiditis encompasses a diverse group of disorders characterized by some form of thyroid inflammation

Classification:

- acute bacterial thyroiditis:
  - suppurated
  - non-suppurated
- De Quervain subacute thyroiditis
- chronic thyroiditis:
  - autoimmune (chronic lymphocitary thyroiditis)
  - wooden Riedl thyroiditis
- specific:
  - lues thyroiditis
  - actinomycotic thyroiditis

Subacute thyroiditis

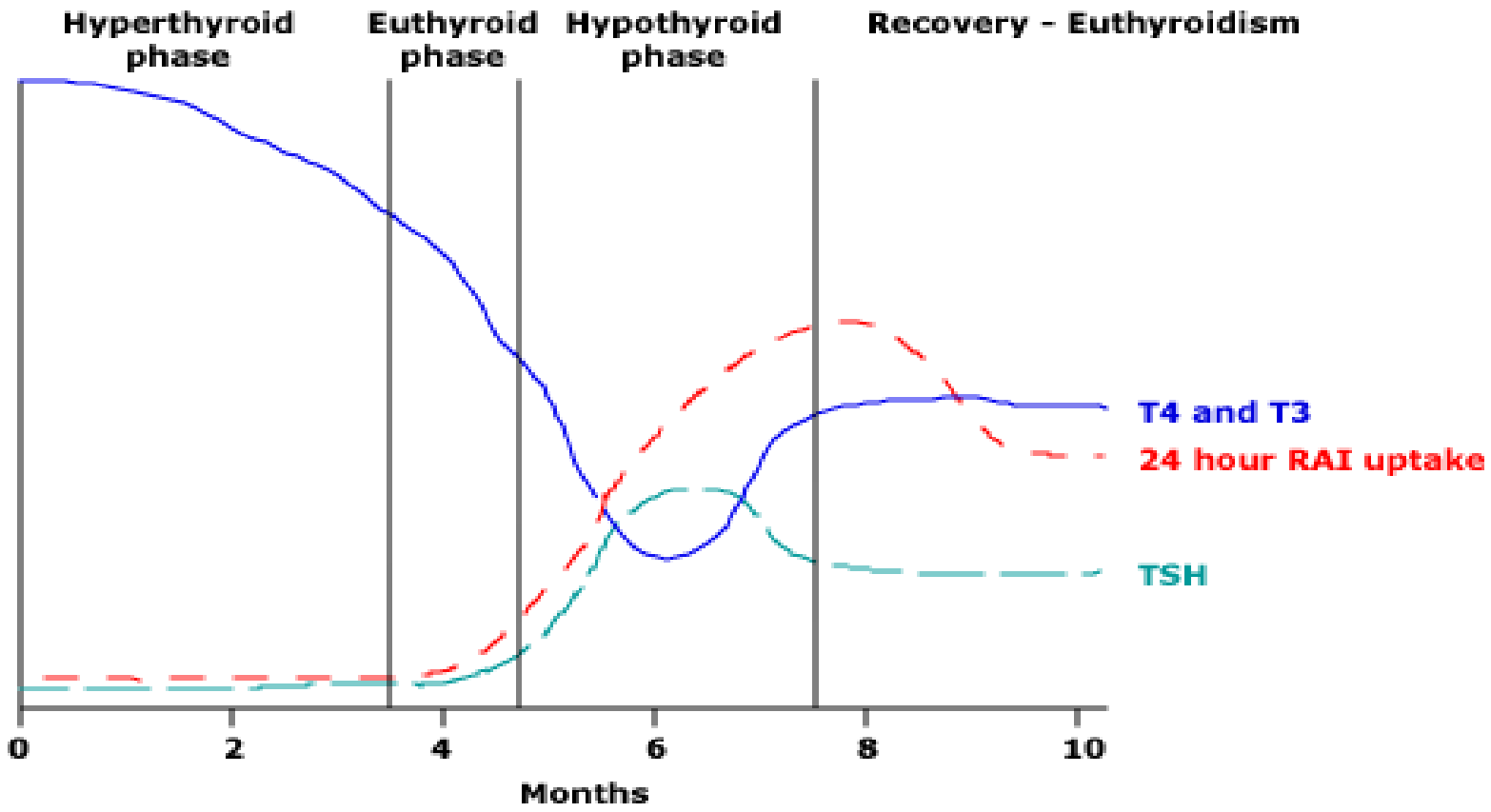
- Subacute thyroiditis is presumed to be caused by a viral infection or a postviral inflammatory process.
- The majority of patients have a history of an upper respiratory infection prior to the onset of thyroiditis (typically two to eight weeks beforehand). The disease was thought to have a seasonal incidence (higher in summer), and clusters of cases have been reported in association with Coxsackievirus, mumps, measles, adenovirus, and other viral infections.

- Thyroid autoimmunity does not appear to play a primary role in the disorder, but it is strongly associated with HLA-B35 in many ethnic groups. A unifying hypothesis might be that the disorder results from a common subclinical viral infection that provides an antigen, either of viral origin or resulting from virus-induced host tissue damage, that uniquely binds to HLA-B35 molecules on macrophages. The resulting antigen-HLA-B35 complex activates cytotoxic T lymphocytes that then damage thyroid follicular cells, because the cells have partial structural similarity with the infection-related antigen.

- Whatever factors initiate subacute thyroiditis, the resulting thyroid inflammation damages thyroid follicles and activates proteolysis of the thyroglobulin stored within the follicles. The result is unregulated release of large amounts of T4 and T3 into the circulation resulting in clinical and biochemical hyperthyroidism. This state lasts only until the stores of thyroglobulin are exhausted because new hormone synthesis ceases, not only because of damage to the thyroid follicular cells but also because of inhibition of thyrotropin (TSH) secretion by the increased serum T4 and T3 concentrations.

As the inflammation subsides, the thyroid follicles regenerate and thyroid hormone synthesis and secretion resume. There is usually a period of rapid evolution through euthyroidism and then into hypothyroidism. The hypothyroidism lasts until the thyroid gland can generate sufficient thyroid hormone synthesis and secretion so that the patient regains normal homeostasis. Each phase typically lasts two to eight weeks with the possible exception of the initial transition through euthyroidism, which may be shorter.

Characteristic course of thyroiditis (painless, postpartum or subacute)



pathology

The thyroid is usually moderately enlarged in subacute thyroiditis. Large-needle thyroid biopsies reveal widespread infiltration with neutrophils, lymphocytes, histiocytes and giant cells, disruption and collapse of thyroid follicles, and necrosis of thyroid follicular cells. Later there may be some fibrosis, but eventually the gland becomes normal. Fine needle aspiration biopsies reveal the same inflammatory cells, plus clusters of follicular cells and masses of colloid.

Clinical manifestations

- pain was the presenting symptom in 96 percent. The onset may be sudden or gradual and may be preceded by an upper respiratory infection. The pain may be limited to the region of the thyroid or radiate to the upper neck, jaw, throat, upper chest, or ears. Pain can be exacerbated by coughing or turning the head. As a result, some patients first consult an otolaryngologist. Fever, fatigue, malaise, anorexia, and myalgia are common.
- The thyroid gland is typically slightly or moderately diffusely or asymmetrically enlarged, and nearly always tender. In some cases, the pain is so severe that the patient cannot tolerate palpation of the neck. Both thyroid lobes are involved from the beginning in most patients, but the pain, tenderness, and enlargement can be unilateral or start on one side and later spread to the other side days or even weeks (so called “creeping thyroiditis”) later.

Clinical manifestations

- Approximately one-half of patients have symptoms and signs of hyperthyroidism, but the neck pain and tenderness usually dominate the illness, and the diagnosis should not routinely be made in their absence. Temperature elevations also can occur.
- The thyroid inflammation and hyperthyroidism are transient, usually subsiding in two to eight weeks, even if the patient is not treated. It may be followed by a period of transient, usually asymptomatic hypothyroidism lasting from two to eight weeks or longer, but recovery is nearly always complete.

- 15 percent of patients eventually develope permanent hypothyroidism requiring **levothyroxine** therapy.
- 4 percent of the patients had a recurrence (6 to 21 years after the initial episode).
- Although the hyperthyroidism is usually mild and transient, it may rarely be associated with serious side effects such as ventricular tachycardia and thyroid storm.

Laboratory findings

- – In addition to thyroid tenderness, nearly all patients have biochemical evidence of hyperthyroidism (high serum free T4 and T3 and low serum TSH concentrations) during the early stages of the illness, even though many have no symptoms of thyroid excess. The serum free T4 and T3 concentrations are usually only mildly elevated, and serum T3 is not typically disproportionately increased, as it is in some patients with Graves' hyperthyroidism. Hyperthyroidism is transient, and may be followed by a period of transient, usually asymptomatic, overt or subclinical hypothyroidism (high TSH and low or low-normal normal serum free T4 and T3).
- The erythrocyte sedimentation rate is usually greater than 50 and may exceed 100
- C-reactive protein may also be elevated.

Other characteristic laboratory findings

- (although not routinely needed to confirm diagnosis) include high serum thyroglobulin concentrations due to release from the thyroid gland, mild anemia, and mild leukocytosis. Liver function tests are also frequently abnormal during the initial hyperthyroid phase and then typically return to normal over the next one to two months as the disease improves. Serum antithyroid peroxidase or antithyroglobulin antibodies are usually undetectable.

Imaging studies

- In patients with subacute thyroiditis and hyperthyroidism, a radioiodine or technetium imaging study will show low uptake (usually less than 1 to 3 percent) or a faint heterogeneous pattern of radionuclide uptake during the hyperthyroid phase (in the absence of previous recent exposure to high iodine-containing radiocontrast agents). On ultrasonography the thyroid appears to be normal or enlarged but is diffusely or focally hypoechogenic regardless of its size.
- Color Doppler sonography shows low flow during the hyperthyroid phase, whereas Graves' hyperthyroidism usually shows enhanced flow. After recovery, thyroid ultrasonography appearance normalizes.

Diagnosis

- Subacute thyroiditis is fundamentally a clinical diagnosis. In most patients, clinical manifestations (the presence of neck pain, often radiating upward to the jaw, marked thyroid tenderness, and a diffuse goiter) are sufficient to establish the diagnosis. Symptoms and signs of hyperthyroidism may or may not be present, but the serum TSH is usually suppressed (typically <0.1 and free T4 and T3 concentrations elevated. Thus, serum TSH, free T4, and T3 should be measured in all patients in whom there is a clinical suspicion of subacute thyroiditis. Also typically are measured an erythrocyte sedimentation rate or C-reactive protein level and obtain a radioiodine or technetium imaging study. A high erythrocyte sedimentation rate C-reactive protein measurement and a low radioiodine uptake (usually less than 1 to 3 percent) during the hyperthyroid phase help confirm the diagnosis.
- In patients with thyroid pain and mild hyperthyroidism, radioiodine or technetium imaging may be deferred and thyroid function monitored. If thyroid function normalizes and pain resolves within several weeks, the diagnosis of subacute thyroiditis is confirmed.

Treatment

- Treatment of patients with subacute thyroiditis should be directed at providing relief for thyroid pain and tenderness and ameliorating symptoms of hyperthyroidism, if present. Some patients need no treatment, because their symptoms are mild or are subsiding by the time they seek medical attention and the diagnosis is established. Thyroid function tests should be monitored every two to eight weeks to confirm resolution of hyperthyroidism, detection of hypothyroidism, and subsequent normalization of thyroid function.
- In the majority of patients, however, antiinflammatory therapy with either a nonsteroidal antiinflammatory drug or **prednisone** is indicated. A reasonable approach is to start with acetylsalicylic acid (**aspirin**, 2600 mg daily) or a nonsteroidal antiinflammatory drug (eg, **ibuprofen** 1200 mg daily) in divided doses. If there is no improvement in two or three days, the nonsteroidal antiinflammatory drug should be discontinued and prednisone (40 mg daily) initiated. Prednisone therapy should result in pain relief in one to two days; if not, the diagnosis should be questioned. In patients with severe pain, prednisone is a reasonable first-line therapy.

- Therapy for hyperthyroidism is not often needed because symptoms, if present, are mild and short-lived. Those few patients who have bothersome symptoms of hyperthyroidism, such as palpitations, anxiety, or tremor, may benefit from treatment with a beta blocker such as 40 to 120 mg propranolol, propranolol LA 80 mg daily, or 25 to 50 mg atenolol daily for a few weeks while they are thyrotoxic.
- Thionamides should not be used because hyperthyroidism is not caused by excess thyroid hormone synthesis. Radioactive iodine is neither effective nor indicated because the uptake of radioiodine is very low.
- Therapy for hypothyroidism is not often needed because symptoms, if present, are usually mild and short-lived. However, if the hypothyroidism is more pronounced (TSH >10 or associated with more than mild symptoms, the patient should be treated with 50 or 100 mcg of levothyroxine (T4) for six to eight weeks (with a goal TSH in the normal range). The T4 should then be discontinued, and the patient reevaluated in four to six weeks to be sure that the hypothyroidism is not permanent.

- **Hashimoto's thyroiditis (chronic autoimmune thyroiditis)**

Hashimoto's thyroiditis

- (chronic autoimmune thyroiditis) is the most common cause of hypothyroidism in iodine-sufficient areas of the world. Thyroid failure is seen in up to 10 percent of the population and its prevalence increases with age. It is characterized clinically by gradual thyroid failure, goiter formation, or both, due to autoimmune-mediated destruction of the thyroid gland involving apoptosis of thyroid epithelial cells. Nearly all patients have high serum concentrations of antibodies against one or more thyroid antigens, diffuse lymphocytic infiltration of the thyroid, which includes predominantly thyroid-specific B and T cells, and follicular destruction.
- The cause of Hashimoto's thyroiditis is thought to be a combination of genetic susceptibility and environmental factors.

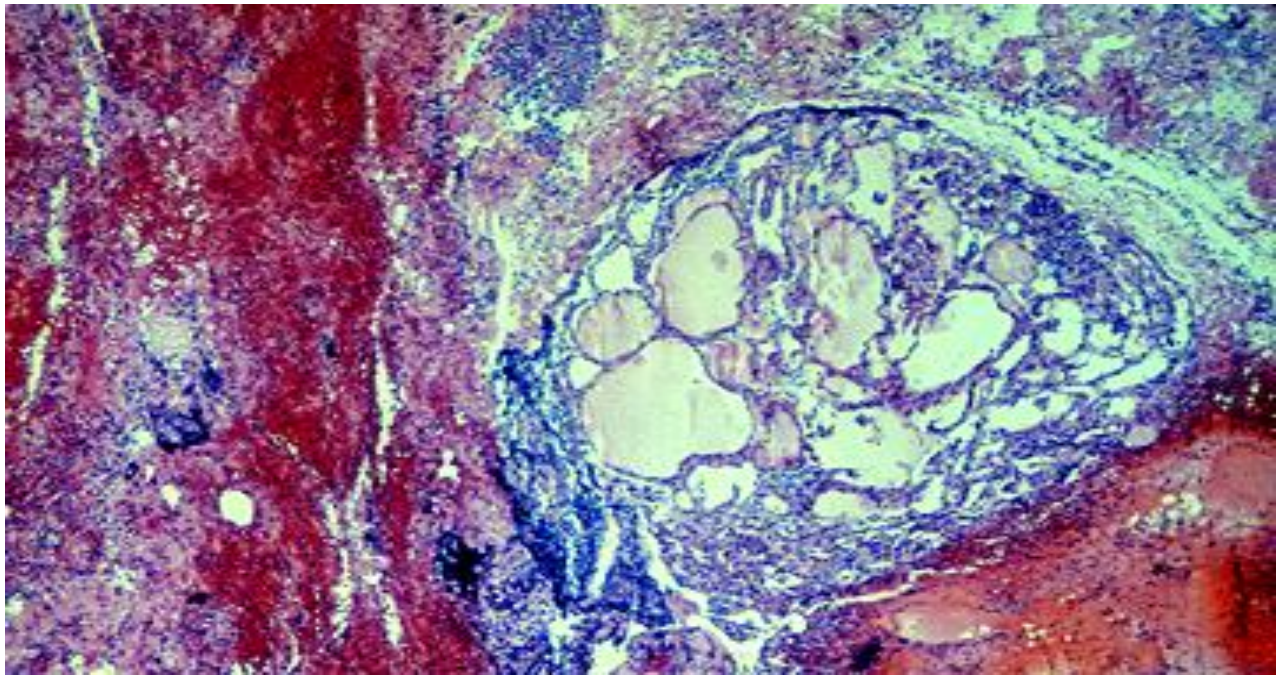
CLINICAL CHARACTERISTICS

- Hence, the two major forms of the disorder are **goitrous autoimmune thyroiditis** and **atrophic autoimmune thyroiditis**, with the common pathologic feature being lymphocytic infiltration and the common serological feature being the presence of high serum concentrations of antibodies to thyroid peroxidase and thyroglobulin. Hashimoto's thyroiditis is primarily a disease of women, with a sex ratio of approximately 7:1; it can also occur in children.

- Variant mild forms of Hashimoto's thyroiditis include silent (or painless) thyroiditis and postpartum thyroiditis, both of which are transient but may be followed years later by thyroid failure.

- While hypothyroidism is the characteristic functional abnormality, the inflammatory process early in the course may involve enough apoptosis to cause thyroid follicular disruption and thyroid hormone release, causing transient hyperthyroidism sometimes referred to as Hashitoxicosis.
- The usual course of Hashimoto's thyroiditis is gradual loss of thyroid function. Among patients with this disorder who have mild (subclinical) hypothyroidism, exhibited as slight increases in TSH and the presence of thyroid antibodies, overt hypothyroidism occurs at a rate of about 5 percent per year. Overt hypothyroidism, once present, is permanent in nearly all cases, except in some children and postpartum women in whom it is often transient.

The characteristic histopathological abnormalities are profuse lymphocytic infiltration, lymphoid germinal centers, and destruction of thyroid follicles. Fibrosis and areas of follicular-cell hyperplasia are also seen in patients with severe disease and the fibroblast reaction may become excessive.



THYROID ANTIGENS

- Several antibodies and antigen-specific T-cells directed against thyroid antigens have been described in chronic autoimmune thyroiditis. The major antigens are:
- Thyroglobulin (Tg)
- Thyroid peroxidase (TPO, formerly known as the microsomal antigen)
- The TSH receptor

- Drug-induced thyroiditis — Patients receiving interferon-alfa, interleukin-2, **amiodarone**, or **lithium** may develop thyroiditis without pain. Its occurrence in patients receiving these drugs does not seem coincidental, but only for interferon-alfa are there sufficient data to indicate and be confident of a causative relationship.
- Interferon-alfa — Thyroid disorders are common in patients with chronic hepatitis C virus (HCV) infection, particularly women. In addition, many patients with HCV infection develop thyroid disease during interferon-alfa therapy.
- The most common interferon-alfa-associated thyroid abnormality is the development of de novo antithyroid antibodies without clinical disease (5 to 15 percent). Approximately 5 to 10 percent of patients develop clinical thyroid disease, including painless thyroiditis, Hashimoto's thyroiditis, or Graves' disease.
- These changes usually appear after three months of therapy, but can occur as long as interferon-alfa is given. The risk of any form of thyroid dysfunction is greater in those patients who have increased serum antithyroid antibody concentrations before initiation of interferon-alfa, a finding that suggests that it in some way exacerbates underlying thyroid autoimmune disease.

- **Lithium** — Patients with depression who are treated with **lithium** have an increased incidence of hyperthyroidism.
- Kinase inhibitors — Tyrosine kinase inhibitors are used to treat a variety of disorders (eg, gastrointestinal stromal tumors, renal cell carcinoma). In euthyroid patients with intact thyroid glands, these agents have been associated with the development of hypothyroidism and an elevated TSH in approximately 50 to 70 percent of patients. Hypothyroidism has been most frequently reported with sunitinib but it appears to be a class effect and probably can occur with any tyrosine kinase inhibitor. Hyperthyroidism, possibly from a destructive thyroiditis, has also been reported.

Fibrous thyroiditis

- — Fibrous thyroiditis, also known as Riedel's thyroiditis or invasive thyroiditis, is characterized by extensive fibrosis and macrophage and eosinophil infiltration of the thyroid gland that extends into adjacent tissues. It is probably a primary fibrosing disorder, and has been reported in patients who also had mediastinal and retroperitoneal fibrosis.
- Affected patients have neck discomfort or tightness, sometimes dysphagia or hoarseness, and a diffuse, although occasionally asymmetric, goiter that is very hard, fixed, and often not clearly separable from the adjacent tissues. Most patients are euthyroid, but a few are hypothyroid, and serum antithyroid antibody concentrations are often high. The diagnosis is established by thyroid biopsy. Patients should be evaluated for evidence of systemic fibrosis in other areas, such as mediastinum and retroperitoneal ares.
- **Prednisone** therapy may alleviate local symptoms. In a small case series, **tamoxifen** appeared to be effective in delaying, or perhaps even helping resolve, the progression of disease. Surgery should only be undertaken after contemplation of the risks and benefits. However, surgery may be indicated to relieve tracheal or esophageal compression and occasionally to exclude carcinoma.