Thyroid Disease

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Thyroid diseases are common endocrine disorders that may seriously affect patients' health and often require lifelong treatment and monitoring. This chapter reviews the most common thyroid problems, with emphasis on clinical presentation, diagnosis, treatment, and follow-up.

Screening for Thyroid Disease

The American Academy of Family Physicians, American College of Physicians, US Preventive Services Task Force, and the Royal College of Physicians all concluded there is not enough evidence to recommend screening in the general population. However, the American Thyroid Association recommends measuring a thyroid-stimulating hormone (TSH) level in all patients at age 35 and every 5 years thereafter, even though they note a serious lack of efficacy data, especially in men and younger women [1]. Laboratory measurement of thyroid function is recommended in certain patient groups who are at higher risk for thyroid disease. The American Association of Clinical Endocrinologists recommends TSH measurement in women of childbearing age before pregnancy or during the first trimester [2]. Patients with atrial fibrillation or hyperlipidemia should have their TSH measured at least once. Annual laboratory measurement of thyroid function is recommended for patients with diabetes or Down syndrome. Patients taking certain medications such as amiodarone and lithium require periodic TSH measurement as these medications may alter thyroid function.

Hyperthyroidism

Thyrotoxicosis is caused by excess thyroid hormone. The prevalence of hyperthyroidism in community-based studies has been estimated at 2 % for women and 0.2 % for men [3]. As many as 15 % of cases of hyperthyroidism occur in patients older than 60 years, of which a large percentage was taking thyroid home preparation [4]. Excluding excess thyroid hormone ingestion, approximately 90 % of hyperthyroidism is caused by Graves' disease. Thyrotoxic nodules and thyroiditis account for almost all other cases [5]. Women are more commonly affected by hyperthyroidism than men, with reported ratios varying from 4:1 to 10:1 [5, 6].

Health Risks

Hyperthyroidism causes or exacerbates several other health problems, with cardiovascular complications being most important. Atrial fibrillation is the most common complication, occurring in 8–22 % of thyrotoxic patients, and these patients are at increased risk of stroke from atrial thromboembolism [7]. Cardiac failure, angina, myocardial infarction, and sudden death have been associated with thyrotoxicosis [8]. Thyroid storm causes multisystem involvement and carries a high risk of mortality (10–75 %) [5]. Calcium and bone metabolism are affected by thyrotoxicosis, leading to osteoporosis and an increased risk of bone fracture. Atrial fibrillation and osteoporosis may occur with even subclinical hyperthyroidism [9]. Certain ethnic groups may suffer less common complications. Periodic paralysis may occur as a result of thyrotoxicosis and is observed mostly in Oriental populations [10].

Family Impact

As with any chronic disease, hyperthyroidism may place stress on the family system. The affected family member may experience emotional labiality, heat intolerance, and fatigue, all of which strain relationships within the family. Hyperthyroidism may be especially stressful prior to diagnosis as the patient and family may not attribute their symptoms to a physiologic illness versus psychological. Symptoms of hyperthyroidism may adversely affect job performance and subsequently produce additional stress and loss of income.

Table 1 Signs and symptoms of thyrotoxicosis (in order of frequency)

Symptoms/signs	Percent of patients
Symptoms	
Nervousness	88
Weight loss	83
Heat intolerance	75
Dyspnea	70
Palpitation	69
Increased sweating	62
Fatigue	58
Tachycardia	51
Eye complaints	49
Weakness	47
Increased appetite	45
Vomiting	44
Swelling of legs	38
Chest pain	36
History of fever	36
Nausea	28
Diarrhea	26
Frequent bowel movements	21
Abdominal pain	20
Swelling in neck	16
Anorexia	13
Constipation	12
Dysphagia	12
Hair loss	4
Signs	
Goiter	96
Skin changes (smooth, moist)	85
Tremor	79
Tachycardia (>100 bpm)	76
Systolic murmur	76
Ocular signs (e.g., lid lag)	60
Brisk deep tendon reflexes	56
Pulse pressure ≥70 mmHg	52
Bruit over thyroid	47
Atrial fibrillation	8
Gynecomastia	7
Splenomegaly	7

Source: See ref. [11]

Clinical Presentation

Symptoms of thyrotoxicosis, arranged in order of frequency, are listed in Table 1, and the chief complaint can be any one of these symptoms. A directed history usually reveals up to eight symptoms, although some patients, especially in the geriatric age group, may report only a few [5, 11].

Patients often report weight loss, even with a history of increased appetite. Heat intolerance is usually described as preferring room temperatures cooler than do other family members or preferring winter to summer. Fatigue and weakness of proximal muscles can be reported as difficulty climbing stairs.

It is of note that abdominal symptoms of vomiting, nausea, and abdominal pain, although previously thought to be rare or present only preceding thyroid storm, may be relatively common [11]. Patients who present with these abdominal symptoms as their chief complaint may be at higher risk of missed diagnosis. Vomiting can occur without nausea and tends to be postprandial. Abdominal pain is usually epigastric or left upper quadrant in location, unrelated to meals, and described as sharp or cramping [11].

Physical findings of thyrotoxicosis are listed in Table 1, and five or more are typically present. Goiter is the most frequent sign, but the enlargement may be only mild or difficult to appreciate, especially when it occupies a substernal location. The skin tends to be warm, moist, and velvety smooth. A fine tremor of outstretched hands is usually present, and deep tendon reflexes are often brisk with a rapid relaxation phase. Lid lag may be present with any cause of thyrotoxicosis; exophthalmos is specific to Graves' disease. Onycholysis may be present, typically of the ring fingers, causing separation of the nail from the distal nail bed and difficulty cleaning the nails (Plummer's nails) [5, 10, 16].

Laboratory Evaluation

Confirmation of clinical thyrotoxicosis is accomplished by measuring thyrotropin (TSH) by a highly sensitive assay and is further substantiated with measurement or estimate of free thyroxine (T_4) and sometimes free triiodothyronine (T_3). These hormones are clinically active only when they are not protein bound. A diagnostic approach

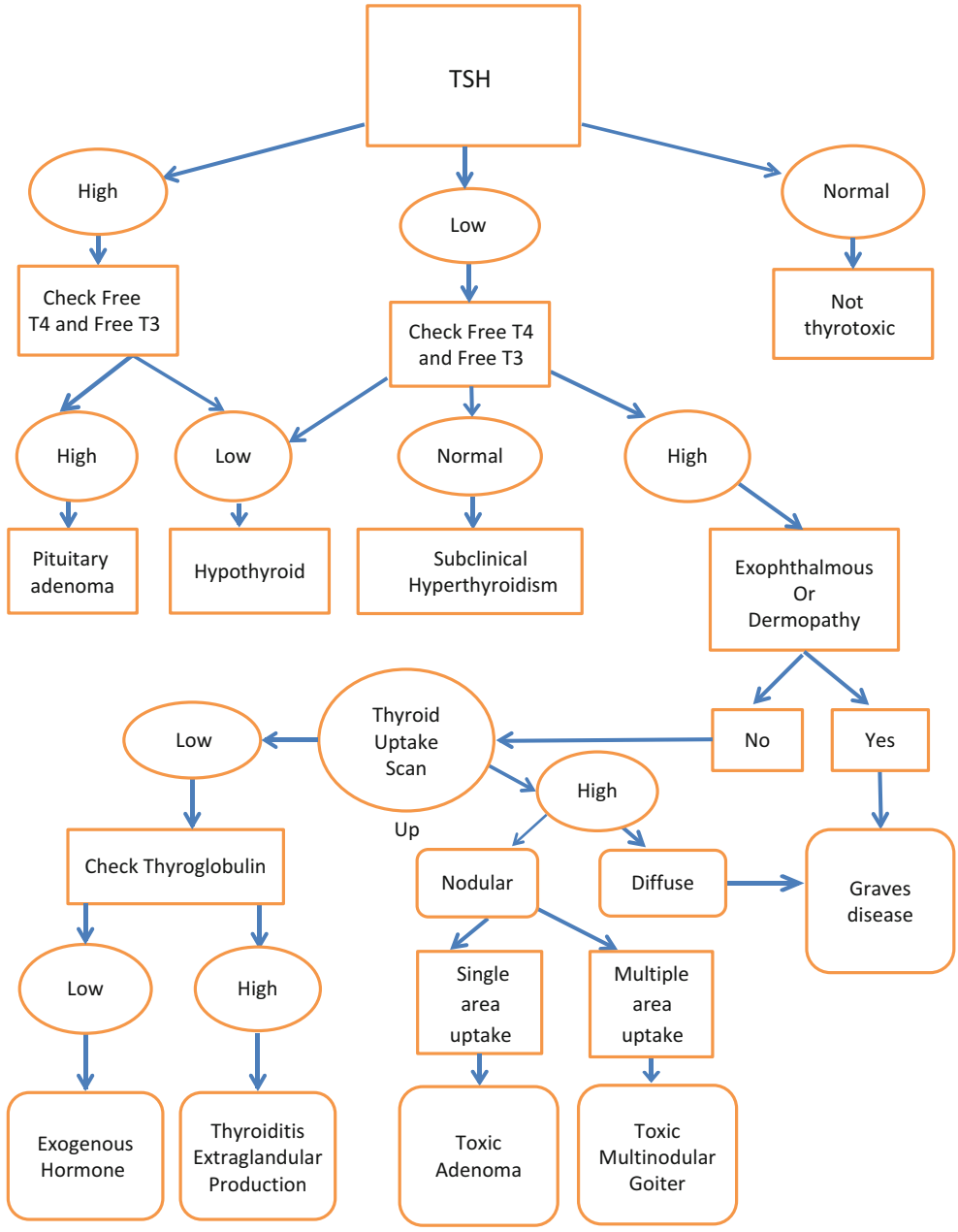

Fig. 1 Diagnostic approach to the patient with thyrotoxicosis

to the patient with thyrotoxicosis is shown in Fig. 1. Along with the TSH, initial tests are usually free T_4 and free T_3. Although the reliability of some methods has been questioned in the past, newer assays of free T_4 and free T_3 are more dependable [5, 12]. Euthyroid patients may have an elevated total T_4 due to excess thyroid-binding proteins, such as found in pregnancy, use of estrogens, or some inherited disorders.

Through pituitary feedback mechanisms, TSH levels inversely follow free T_4 levels. Measurement of TSH by a highly sensitive assay in

patients with hyperthyroidism yields a value far below the normal range and helps confirm the diagnosis. The sensitive TSH is especially useful in patients with concomitant illnesses or on medications that can alter T_4 [12]. Because TSH is a more sensitive measure of thyroid status, patients may have an abnormally low TSH with a normal free T_4. They are considered to have subclinical hyperthyroidism [5, 9]. TSH can also be moderately low as a result of nonthyroidal illness or medications (glucocorticoids and dopamine) and is occasionally low in healthy people, particularly the elderly [13]. The TSH level in these settings is usually not less than 0.1 μU/mL. When the TSH level is less than the lower limit of a sensitive assay (undetectable), thyrotoxicosis is usually present [5]. Rarely, a TSH-secreting adenoma causes hyperthyroidism with an elevated TSH.

When TSH is low but free T_4 is normal, measurement of free T_3 should be obtained and, if elevated, confirms clinical thyrotoxicosis. This condition, known as T_3 toxicosis, occurs occasionally in patients with early Graves' disease or a thyrotoxic nodule [5, 10].

Nuclear medicine scans of the thyroid are useful for assessing thyroid size to determine if thyroid nodules are functioning (hot) or nonfunctioning (cold) and to measure the level of thyroid function (thyroid uptake). Of the radionuclides available for thyroid scans, iodine 123 (^{123}I) is optimal. Technetium may also be used for thyroid imaging, but measurement of function is less reliable, as a nonfunctioning nodule by the ^{123}I scan may demonstrate function with technetium [5].

Graves' Disease

The disease described by Robert Graves in 1835 is the most common cause of hyperthyroidism [5]. It is caused by an autoimmune process, closely related to chronic lymphocytic (Hashimoto's) thyroiditis. The onset of Graves' disease may follow some physical or psychological stress, and a family history of thyroid disease is often present [5, 10].

Signs and Symptoms

All the clinical manifestations of thyrotoxicosis may be present in Graves' disease, with additional specific findings of ophthalmopathy and dermopathy. A diffuse goiter occurs in most patients and may cause neck swelling or dysphagia. On palpation, the thyroid is nontender and somewhat soft. Eye problems occur in more than 50 % of patients and include pressure sensation, irritation, gritty feeling, lacrimation, a change in appearance, and occasional blurred vision or diplopia. The exophthalmos occasionally causes marked eye irritation or even blindness. Dermopathy occurs in 1–2 % of patients and causes raised, firm, nontender, intradermal nodules on the anterior surfaces of the lower legs. Clubbing of the nails (acropachy) is a rare manifestation of Graves' disease [5, 10].

Diagnosis

Graves' disease is diagnosed by confirming hyperthyroidism with thyroid function tests (free T_4), along with one or more physical findings specific to the disease. If a goiter is present without exophthalmos or dermopathy, Graves' disease may be difficult to distinguish from subacute painless thyroiditis or postpartum thyroiditis. A reliable history of chronic hyperthyroid symptoms strongly suggests Graves' disease, and an elevated thyroid uptake confirms this diagnosis when it remains in doubt [5, 10]. Thyrotropin receptor (TSH-R) antibodies are present in most patients with Graves' disease, but they are of limited diagnostic value. High titers of these antibodies may identify those patients who are unlikely to go into remission. Measurement of TSH-R antibodies in pregnant patients with thyrotoxicosis may be useful [5].

Treatment

Therapy of Graves' disease is directed toward controlling the effects of excess thyroid hormone and reducing the production of additional

hormone [13]. Beta-blockers are especially effective in controlling the tachycardia, tremor, and other symptoms related to excess hormone. Atenolol is often preferred because it has the advantages of single daily dosing and beta-1 selectivity. Alternatively, propranolol is begun at 20–40 mg 2–4 times daily and increased every few days until the heart rate is within the normal range [10]. When beta-blockers are contraindicated, diltiazem or clonidine may be effective [14, 15]. Controlling hormone production may be accomplished with antithyroid medications, radioiodine ablation, or surgery. Choice of treatment is influenced by the clinical presentation, the age of the patient, and the patient's ability and willingness to comply with a treatment regimen [5, 10].

Antithyroid medications available in the United States to control thyroid hormone production are the thionamides, methimazole, or propylthiouracil. In addition to blocking production of thyroid hormone, these medications may alter the course of the disease via their immunosuppressive effects [16]. Reported remission rates vary widely and are probably higher in patients with less severe hyperthyroidism, short duration of illness, and small goiter. The duration of treatment is usually 6 months to 2 years. The remission rate can be as high as 60 % if treatment is continued for 2 years. Failure to achieve remission after 2 years of treatment is an indication for alternate therapy [5, 10, 16].

Initial adult dosage of methimazole is 20–30 mg/day divided into two doses. In patients with severe hyperthyroidism and a large goiter, the higher dose is warranted. Euthyroid status, determined clinically and with thyroid function tests (T_4 and T_3), is usually achieved within 4–6 weeks, and the dosage is reduced incrementally every 4–6 weeks to a maintenance dose of 2.5–10 mg/day given in a single dose. TSH is not useful for following the response to treatment, as it may remain suppressed for months after T_4 and T_3 normalize. The initial dose of propylthiouracil is usually 300 mg/day, and maintenance is 50–100 mg/day. Both must be divided into three doses [5, 10]. Either of these drugs may cause rash, leukopenia, and (rarely) agranulocytosis. Patients should be cautioned about these side effects. Methimazole has the advantages of lower risk of agranulocytosis, a longer half-life allowing usage on a once-a-day schedule, and more rapid return to euthyroid status. Propylthiouracil is preferable during pregnancy, lactation, or thyroid storm [5, 10]. Patients with mild hyperthyroidism and small goiters or those with goiters that shrink during antithyroid medication therapy may go into remission with a prolonged course of antithyroid medications.

Iodine 131 ablation may be used for definitive treatment for patients with more severe hyperthyroidism and large goiters to permanently destroy thyroid tissue sufficiently to reduce hormone production to normal levels. This option has the advantage of low cost and low complication rate. This treatment may be used initially in patients with mild thyrotoxicosis. Patients who are elderly or have severe thyrotoxicosis should first be treated with antithyroid medications because ^{131}I ablation can induce a temporary exacerbation of thyrotoxicosis or thyroid storm [10]. The amount of radiation used can be calculated based on the patient's weight, gland size, and thyroid uptake. A major disadvantage of this treatment is the high prevalence of hypothyroidism (>90 %), which continues to increase with the passage of time [5]. Therefore, a patient's ability to comply with lifelong replacement therapy should be considered when choosing this treatment. Pregnancy is a contraindication to ^{131}I.

Subtotal thyroidectomy is an alternate method of permanently controlling thyroid hormone production. This treatment is indicated when the goiter is large, particularly if obstructive symptoms are present. Surgery is also indicated in children who fail a trial of antithyroid medication. The disadvantages of surgery include the cost and risk of surgical complications. Following surgery for Graves' disease, hypothyroidism has been reported in 53 % of patients and recurrence of hyperthyroidism in 3.4 % [10].

Follow-Up

Regardless of the treatment used, Graves' disease requires lifelong monitoring. Patients treated with antithyroid medications who go into remission

must be followed for possible relapses and are at a small risk of late hypothyroidism. After treatment with ^{131}I ablation or surgery, patients require chronic periodic monitoring for development of hypothyroidism. Once hypothyroidism occurs, lifelong hormone replacement is necessary [5, 10].

Thyrotoxic Nodule

An autonomously functioning thyroid nodule may cause thyrotoxicosis with typical hyperthyroid symptoms. Physical examination reveals a thyroid nodule, and findings specific to Graves' disease are absent. The diagnosis is confirmed with an elevated free T_4, low TSH, and a hot nodule on radioiodine scan. Fine-needle aspiration is indicated if the nodule is not hot on nuclear medicine scan, as with other nontoxic nodules.

Treatment is with ^{131}I ablation or occasionally surgery. Antithyroid medications may be used but are not typically prescribed for thyrotoxic nodules. Hypothyroidism following ^{131}I ablation is less common than with Graves' disease, although a 40 % long-term prevalence of hypothyroidism has been reported [17]. Indications for surgery include a thyrotoxic nodule that is very large or progressively enlarging or other signs suggestive of thyroid cancer [5].

The nodule may persist after ablation treatment, and ongoing monitoring by physical examination is needed to identify any increase in size. Should the nodule or adjacent tissue enlarge, further evaluation for possible thyroid cancer is required. Periodic monitoring for possible hypothyroidism also is necessary.

Thyroiditis

Thyroiditis is defined as an inflammatory process involving the thyroid gland. This inflammation may cause thyrotoxicosis due to unregulated release of thyroid hormone from an injured gland. There are several types of thyroiditis, each with a different clinical picture; three are discussed below. Hashimoto's thyroiditis is discussed in the next section, and postpartum thyroiditis is discussed in the section on pregnancy. Measurement of ^{123}I thyroid uptake is useful in any patient with thyrotoxicosis and suspected thyroiditis. Elevated free T_4 with diminished thyroid uptake confirms thyrotoxicosis due to thyroiditis.

Subacute painful (granulomatous) thyroiditis is probably caused by a viral infection and is the type of thyroiditis that most commonly results in thyrotoxicosis. Patients present with an exquisitely tender, firm, asymmetric nodular thyroid gland. They have symptoms of neck pain, a flu-like syndrome, and symptoms of thyrotoxicosis. The erythrocyte sedimentation rate is elevated, and antithyroid antibodies are absent. These patients usually go through four phases: (1) hyperthyroidism lasting 3–6 weeks, (2) euthyroid status for a few weeks, (3) hypothyroidism lasting weeks to months, and (4) euthyroid state again. The clinical diagnosis is usually made during the hyperthyroid phase and is confirmed with an elevated free T4 and decreased uptake on ^{123}I scans. Treatment of inflammation is accomplished with aspirin, other nonsteroidal anti-inflammatory agents, or corticosteroids (prednisone 20 mg twice daily for 1 week then tapered over 2–4 weeks). Patients may require β-blocker therapy to control symptoms and tachycardia initially, but there are usually no long-term sequelae requiring treatment or monitoring [5, 18].

Subacute painless (lymphocytic) thyroiditis is an autoimmune process that may cause thyrotoxicosis. Physical examination usually reveals a mildly enlarged thyroid gland that is somewhat firm and nontender, although nearly 50 % of patients have no goiter. Antibodies to thyroid peroxidase are present in about 50 % of patients. These patients may go through the same four phases as subacute painful thyroiditis, but the euthyroid phase preceding hypothyroidism may be brief or absent. Some patients do not return to euthyroid status after hypothyroidism occurs and require chronic thyroid hormone replacement [5, 18].

Acute thyroiditis, caused by a bacterial infection, is a rare condition in developed countries because of the availability of antibiotic therapy. Patients present with acute thyrotoxicosis, fever,

and a tender, enlarged thyroid gland. Treatment is directed toward controlling effects of excess thyroid hormone with beta-blockers and treating the infection with broad-spectrum antibiotics. Needle aspiration for culture is indicated, and abscess drainage may be necessary [5, 18].

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is defined by low or undetectable serum thyroid-stimulating hormone (TSH) levels, with normal levels of free T4 and free T3. Subclinical hyperthyroidism can be divided into two categories: low but detectable TSH levels (0.1–0.4 mIU per L) and suppressed TSH levels (less than 0.1 mIU per L) [19]. Subclinical hyperthyroidism may be exogenous as a result of intentional administration of thyroid hormone to suppress thyroid malignancy or unintentional excessive hormone therapy in patients with hypothyroidism. It may also result from endogenous overproduction of thyroid hormone such as from Graves' disease, autonomous functioning thyroid adenoma, toxic multinodular goiter, and subacute/painless/postpartum thyroiditis. Subclinical hyperthyroidism should be differentiated from other causes of low TSH levels that are not related to relative thyroid overactivity, such as the use of certain drugs (dopamine and glucocorticoids), nonthyroidal illness (euthyroid sick syndrome), pituitary causes (TSH deficiency), hypothalamic causes (thyrotropin-releasing hormone deficiency), and psychiatric conditions, especially affective disorders [20].

Most patients with subclinical hyperthyroidism will not progress to overt hyperthyroidism. Cardiovascular effects of subclinical hyperthyroidism include an increase in average heart rate, increased risk of atrial arrhythmias, increased left ventricular mass, and reduced heart rate variability [20–22]. Subclinical hyperthyroidism may reduce bone mineral density (BMD), particularly in cortical bone. Patients with subclinical hyperthyroidism may experience increased signs and symptoms of adrenergic overactivity, particularly those younger than 50 years [20]. Possible associations between subclinical hyperthyroidism and quality of life parameters, cognition, and increased mortality rates are controversial [20]. The effectiveness of treatment in preventing these conditions is unknown. There is no consensus regarding screening for subclinical hyperthyroidism in the general population.

Hypothyroidism

Hypothyroidism, a deficiency of thyroid hormone, can be caused by several conditions that result in the same clinical picture. The most common causes of hypothyroidism are autoimmune thyroid diseases, including Hashimoto's thyroiditis, and previous treatment for Graves' disease. Other causes of thyroiditis, congenital hypothyroidism, and central (secondary) hypothyroidism are uncommon.

Approximately 1–2 % of the general population has spontaneous hypothyroidism: 1.9 % of the female population and 0.1 % of the male population [6]. Hypothyroidism is more common with advancing age, affecting 6.9–7.3 % of patients aged 55 or over [23, 6]. Women are affected 10 times more frequently than men. Congenital hypothyroidism occurs in 1/3,000 to 1/4,000 live births in the United States [24].

The US Preventive Services Task Force and the American Academy of Family Physicians do not recommend routine screening for hypothyroidism in asymptomatic adults [25].

Health Risks

Severe hypothyroidism may lead to coma and death if untreated. Hypothyroidism can cause bradycardia, hearing impairment, carpal tunnel syndrome, and hypercholesterolemia with increased risk of atherosclerotic heart disease. Dementia, depression, and suicide can be sequelae of hypothyroidism. Hashimoto's thyroiditis may be associated with primary thyroid lymphoma [19]. Elderly patients are at increased risk because concomitant illnesses are common and because the symptoms of hypothyroidism may remain unrecognized [23].

Family Issues

The depression associated with hypothyroidism may have a devastating effect on the family. Withdrawal, vegetative disturbances, apathy, and loss of motivation can affect the entire family unit. This situation is especially a problem when the diagnosis is delayed.

Clinical Presentation

The most common symptoms of hypothyroidism are cold intolerance and fatigue [25]. Other symptoms include generalized weakness, fatigue, memory loss or slowed thinking, intolerance to cold, dry skin, hair loss, hoarseness, dyspnea, anorexia, deafness, chest pain, arthralgia, and facial or peripheral edema. A modest weight gain of approximately 10 pounds is typical, but patients may actually lose weight early in the disease process due to anorexia [1]. Constipation is a common complaint. Depression is often the presenting symptom, and hypothyroidism must be considered during any depression work-up [26, 27] (see ▶ Chap. 32, "Anxiety Disorders"). Women may have heavy, prolonged menstrual periods that can lead to severe anemia [5].

Periorbital edema, peripheral edema, and pale, thick, dry skin are often the first physical signs noted. Hyperkeratosis of the knees and elbows is also common. Diastolic hypertension may be present. Delayed relaxation phase of deep tendon reflexes is common but may be subtle. When hypothyroidism is severe, mucopolysaccharides deposit in subcutaneous tissue, causing the nonpitting edema known as myxedema. Pleural and pericardial effusions, cardiomegaly, bradycardia, and prolonged QT interval are possible cardiac manifestations [5].

Laboratory Evaluation

Primary hypothyroidism is diagnosed by finding an elevated TSH and a low free T_4 [25] (Fig. 2). Patients may have other lab abnormalities including elevated C-reactive protein, hyperprolactinemia, hyponatremia, increased creatinine kinase, increased serum lipids, proteinuria, and normocytic anemia [25]. Secondary hypothyroidism is characterized by a normal or low serum TSH and a low serum T4 (Fig. 2).

Treatment

Oral synthetic L-thyroxine is the treatment of choice for hypothyroidism [12] [19, 25, 28]. The usual starting dosage is approximately 75 μg/day, but patients older than 50 years and patients with heart disease are started at a much lower dose (25 μg/day). The patient should be instructed to take the medication on an empty stomach (1 h) and should not be taken with other medications such as bile acid resins, proton pump inhibitors, calcium carbonate, and ferrous sulfate [25]. The TSH is measured every 6 weeks, and the dosage of thyroxin is adjusted upward by 25 μg/day until the TSH is within the normal range, indicating the patient has returned to a euthyroid state. The target dose for most patients is approximately 1.6–1.7 μg/kg/day. Most forms of hypothyroidism are lifelong problems, and continued replacement is necessary. Once the patient is on a stable dose, the TSH level should be assayed annually to monitor appropriateness of replacement therapy [12]. Overreplacement with T4 can cause hyperthyroidism and its complications. Noncompliance with levothyroxine therapy is the most common cause of difficulty in obtaining and maintaining a patient's TSH in the therapeutic range [25].

The majority of evidence does not demonstrate a benefit of combination T4 and T3 therapy [28]. Temporary treatment with T3 may be appropriate in some patients; however, further studies are needed before that can be recommended.

Subclinical Hypothyroidism

Subclinical hypothyroidism is defined as the presence of a high TSH with a free T_4 in the normal range. Some authors feel these patients are functionally hypothyroid relative to their own bodily requirements [12, 28] [29]. There is still some

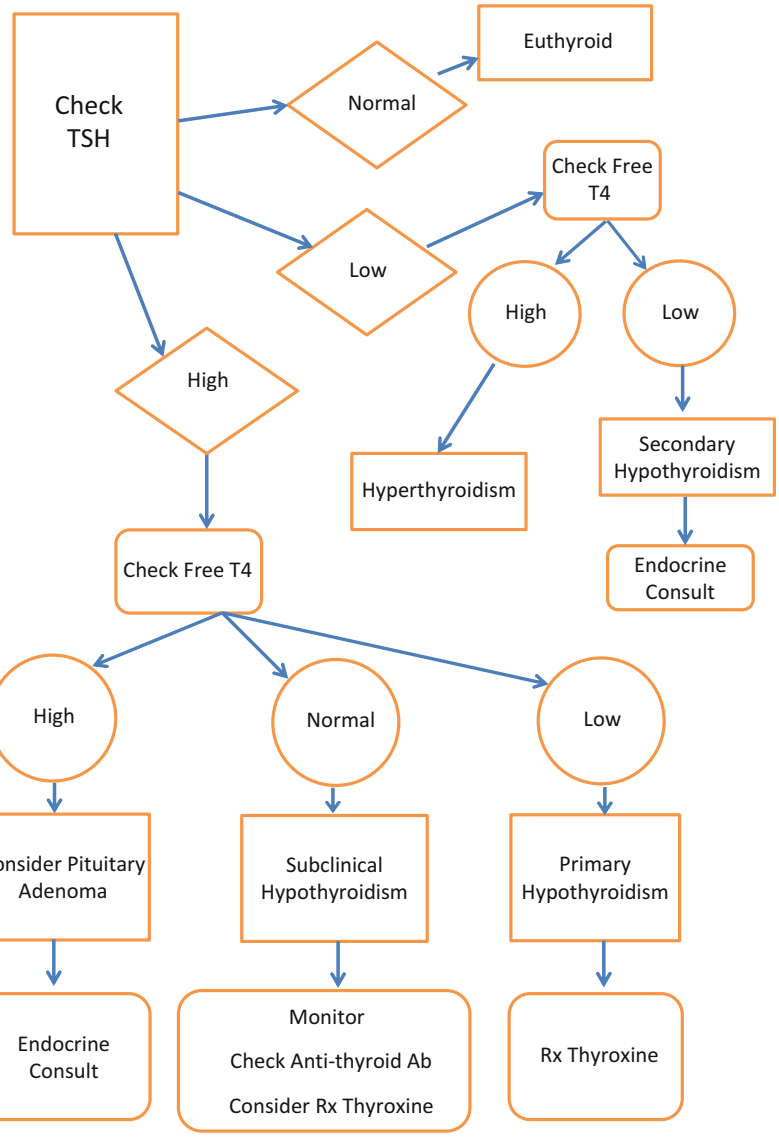

Fig. 2 Evaluation for hypothyroidism [11]

debate about whether to treat subclinical hypothyroidism. Patients often feel better with therapy, and treatment is usually indicated, especially if antithyroid antibodies are present [3]. Asymptomatic patients who have mild TSH elevation (<10 μU/mL), negative antithyroid antibodies, and no goiter may be followed without replacement [5, 19]. Since subclinical hypothyroidism may be associated with reversible hypercholesterolemia, depression, and atherosclerosis, treatment is warranted for patients with these conditions as well as infertility or pregnancy [25, 26, 30, 31].

Hashimoto's Thyroiditis

Hashimoto's thyroiditis was first described in 1912 in four patients with lymphocyte infiltration, fibrosis, and follicular cell degeneration. It causes most cases of adult-onset hypothyroidism in iodine-sufficient areas of the world [6, 18]. The

etiology of the disease is autoimmune, with high serum concentrations of antibodies to thyroid peroxidase and thyroglobulin usually present [18, 29]. Like most autoimmune diseases, there is a genetic predisposition. It is most common in women (8:1) and is usually diagnosed between the ages of 30 and 50. Its incidence is increasing in developing countries [18].

Signs and Symptoms

Patients usually present with a painless, diffuse, firm goiter. Patients may complain of tenderness or fullness of the anterior neck. Dysphagia and hoarseness are occasionally present. Although hyperthyroidism is found in up to 5 % of patients during the acute stages of the disease, hypothyroidism with its various signs and symptoms is more common [19]. The presence of pain suggests the development of a primary B-cell lymphoma, a cancer associated with chronic autoimmune thyroiditis [5].

Diagnosis

The diagnosis is suspected in patients with a characteristic goiter and is confirmed in 90 % of cases by finding antibodies to thyroid peroxidase. Antithyroglobulin antibodies are also present in up to 70 % of patients, but they are rarely present alone. Therefore, this latter assay is not usually necessary for diagnosis [29]. Free T_4 and the TSH level should be obtained to determine thyroid function [18, 29]. If the goiter is very large, lobulated, or painful, fine-needle aspiration or biopsy may be indicated [5].

Treatment

Treatment of hypothyroidism is described above and requires lifelong replacement. Thyrotoxicosis usually does not occur with this type of thyroiditis, and if present is of short duration requiring only symptomatic treatment. Graves' disease may precede or follow this illness and require additional treatment.

Congenital Hypothyroidism

Thyroid dysgenesis is the cause of congenital hypothyroidism in 80 % of patients, and various problems with thyroid hormone production and regulation account for the rest. Severe growth and mental retardation (cretinism) can occur, but these sequelae are avoided if replacement therapy with levothyroxine is started within the first 3 months of life. Undiagnosed congenital hypothyroidism has become rare in industrialized countries owing to neonatal screening. Transient perinatal hypothyroidism may result when mothers are given iodine or iodine-containing contrast agents [24].

Euthyroid Sick Syndrome

Many severely ill patients without signs or symptoms of thyroid dysfunction have a low T_3 level or have T_3 and T_4 levels below normal range. Free T_4 is usually normal if measured by a reliable, sensitive assay, and TSH is also usually normal. This so-called euthyroid sick syndrome is not indicative of true tissue hypothyroidism, and replacement is unnecessary unless the TSH level becomes markedly elevated (>20 μU/mL) [32].

Thyroid Nodules and Thyroid Cancer

Benign thyroid nodules are frequently encountered in primary care. They are estimated to occur in 4–8 % of the adult population. In contrast, clinically significant thyroid cancer is infrequent, comprising only 1 % of all malignancies and ranking 35th among causes of cancer death. Clinically insignificant thyroid cancers are more common, with American autopsy studies revealing a prevalence of 6–13 % [33].

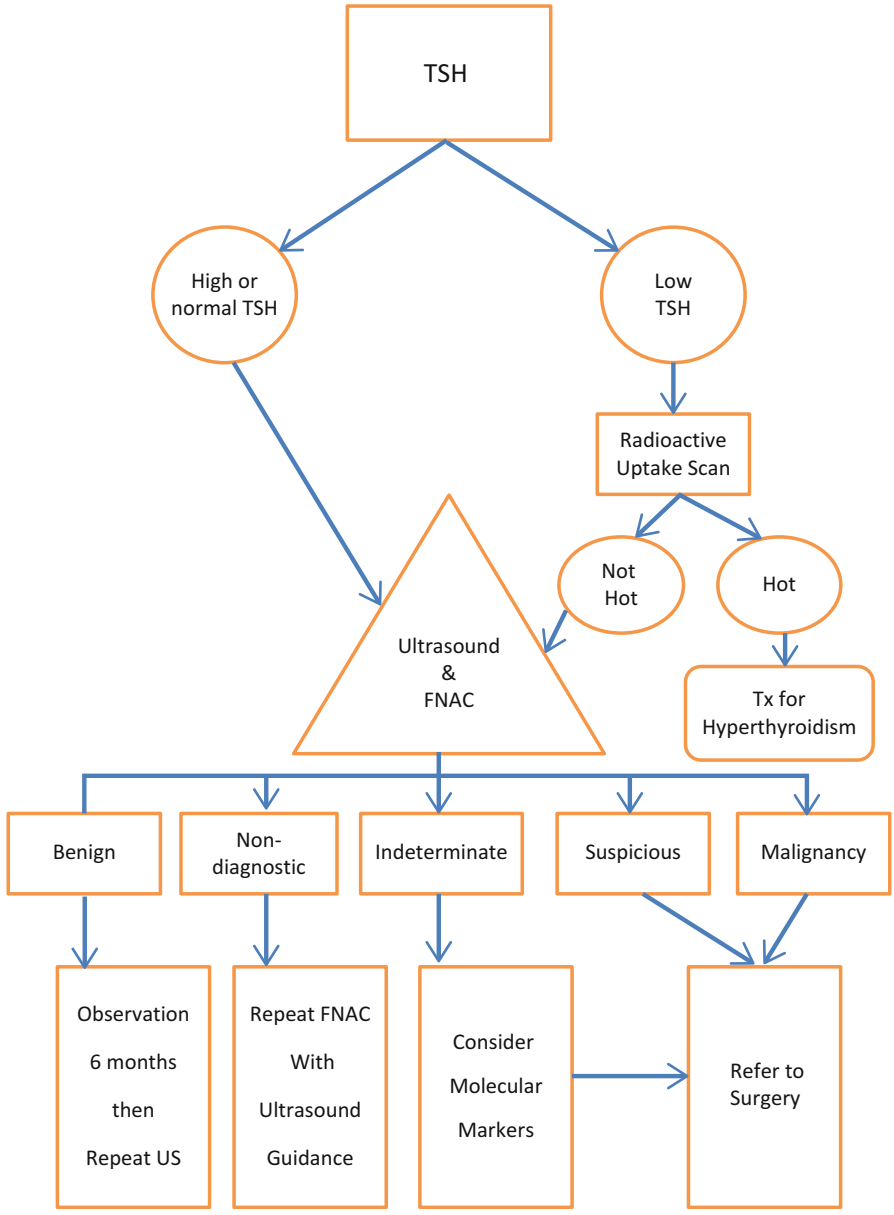

Fig. 3 Evaluation of thyroid nodule (palpable or incidental)

Health Risks and Family Issues

Providing cost-effective yet thorough management for patients with thyroid nodules represents a distinct challenge to family physicians (Fig. 3). Although thyroid nodules carry a low risk of mortality due to thyroid cancer, patients and their families must struggle with the knowledge that a potentially malignant growth is present. The anxiety produced by this fear not only causes stress in the patient but also has major implications for the family. Therefore, the evaluation should reveal adequate information not only to satisfy the physician but to alleviate the fears of patients and their family members.

Table 2 Clinical factors suggesting malignancy in thyroid nodules

High probability
Rapid growth of nodule
Vocal cord paralysis
Fixation to adjacent tissue
Enlarged regional lymph node(s)
Very firm nodule
Family history of multiple endocrine neoplasia type II (MEN-II) or medullary carcinoma
Distant metastases (lungs or bones)
Moderate probability
Age <15 years
Age >70 years
History of neck irradiation
Diameter of nodule >4 cm
Male sex and solitary nodule

Evaluation

Table 2 lists the findings that indicate high and moderate risks of cancer. When two or more of these factors are found, the probability of thyroid cancer is high. Laryngoscopy to evaluate vocal cord function is indicated, especially if any hoarseness or voice change has occurred. A history of neck irradiation increases the risk of both benign and malignant thyroid nodules. Multiple thyroid nodules suggest a benign process.

Laboratory Studies

Thyroid function tests and the TSH assay are useful for confirming the clinical impression of thyroid status. Thyrotoxic nodules are only rarely malignant [5, 34]. Measurement of antibodies to thyroid peroxidase is useful for identifying autoimmune thyroiditis when there is also diffuse enlargement of the gland. A calcitonin assay is important in patients with a family history of multiple endocrine neoplasia type II (MEN-II) or medullary carcinoma, as calcitonin is usually elevated under these conditions. Genetic testing and calcitonin elevation may identify family members with this type of thyroid cancer before clinical manifestations appear [5, 29, 33].

Work-Up

The work-up of a solitary nontoxic thyroid nodule is outlined in Fig. 3. The evaluation begins with a TSH. Patients with a low TSH need a radionuclide thyroid scan. A palpable nodule that corresponds to an area of tracer uptake requires no cytologic evaluation; however, a thyroid ultrasound may be considered. According to the American Thyroid Association (ATA) Guidelines, all thyroid nodules or suspected thyroid nodules in patients with an elevated or normal TSH should have ultrasonography to document location, number, size, and appearance of the nodule(s) followed by fine-needle aspiration and cytology (FNAC) [34]. Other experts maintain that all nodules should be examined through ultrasound, regardless of the TSH [35]. FNAC has become the initial procedure of choice because it is the most accurate and most cost-effective [34]. The FNA technique is relatively simple and low risk [5, 33], and its sensitivity is reported to be more than 90 % [36, 37]. The most worrisome limitation of FNAC is a false negative that may cause a malignancy to be missed, although the false-negative rate has been less than 10 % in most studies and in one study as low as 0.7 %. There is particular difficulty differentiating follicular adenoma from follicular carcinoma with FNAC, as finding evidence of invasion is required to diagnose the latter. A skilled and experienced cytopathologist is required for reliable results.

Results of FNAC are classified into five categories: (1) malignant when malignant cells are identified, (2) benign when adequate benign glandular tissue is present, (3) nondiagnostic when the biopsy tissue does not meet specific criteria for cytologic adequacy, (4) indeterminate which can be a follicular neoplasm (Hurthle cell neoplasm) or atypia, and (5) suspicious for papillary thyroid cancer. Results read as nondiagnostic require the FNAC to be repeated using ultrasound guidance [36].

Ultrasonography can be used to determine if a thyroid nodule is solid or cystic, but this finding does not completely differentiate benign from malignant nodules. Studies have demonstrated that 9–14 % of cystic nodules contain cancer compared to 10–20 % of solid nodules being cancerous [34]. Cystic degeneration occurs in

25 % of papillary carcinomas; therefore, the characteristic appearance of the nodule on ultrasonography does not determine whether or not a biopsy is indicated. Ultrasonography may be used to monitor and follow the characteristics and size of a nodule and to evaluate for metastasis.

Management

The decision regarding when to remove a thyroid nodule surgically should take into account several factors, including clinical findings, availability of FNAC with cytopathologic support, degree of anxiety of the patient and family, and ability to have reliable long-term follow-up. ATA Guidelines are as follows: (1) Surgery is recommended for patients with FNAC results demonstrating malignant cells or suspicion for malignant cells. (2) Observation and serial ultrasound examinations 6–18 months are recommended for nodules with benign FNAC. Should the nodule increase in size, repeat FNAC or surgery is indicated. (3) Repeat the FNAC if the initial results are nondiagnostic. Consider surgery if the second FNAC is also nondiagnostic. (4) Consider surgery or repeat the FNAC for a persistent nodule after aspiration of a cyst. (5) Recurrent cystic nodules with benign cytology should be considered for surgery or percutaneous ethanol injection [34].

Routine suppression of benign thyroid nodules with thyroid hormone replacement is not recommended in iodine-sufficient populations. Thyroid nodules associated with Hashimoto's thyroiditis have been shown to respond to suppression [5].

Thyroid Cancer

Thyroid cancer is divided into two main types: differentiated thyroid cancer (DTC) and poorly differentiated thyroid cancer. DTC arises from thyroid epithelial cells and accounts for the vast majority of thyroid cancer and is associated with a more favorable prognosis. Surgery is the treatment of choice for all thyroid carcinomas when excision is possible [34, 36].

Differentiated Thyroid Cancer Cell Types

1. Papillary carcinoma accounts for 85 % of all thyroid cancers. The tumor is slow growing, and there is good long-term survival if surgical removal is performed while the cancer is still confined to the thyroid gland. Papillary carcinoma spreads by lymphatic means.
2. Follicular carcinoma accounts for about 10 % of all thyroid cancers. It is slightly more aggressive than the papillary variety and spreads by the hematogenous route. A subcategory of follicular carcinoma is the Hurthle cell type, which is more aggressive and more common in iodine-deficient countries [34].
3. Medullary carcinoma accounts for only 2–5 % of thyroid cancers. Most of these lesions are sporadic, but some are familial; 20 % are part of the MEN-II syndrome, which has an autosomal-dominant inheritance pattern. The latter can be identified early with elevated calcitonin levels and genetic testing. Screening with these tests should be performed on all family members if MEN-II or familial medullary carcinoma is diagnosed. If medullary carcinoma is not diagnosed prior to a palpable mass being present, the cure rate is less than 50 % [33, 34, 38].

Undifferentiated Thyroid Cancer Cell Type

1. Anaplastic thyroid carcinoma is the most aggressive type but accounts for only 2–7 % of cases. It has the worst prognosis of any thyroid cancer, with a median survival time of 4–7 months and a 5-year survival rate of only 4 %.

Near-total or total thyroidectomy is the procedure of choice if the thyroid cancer is greater than 1 cm. Lobectomy may be appropriate for less than 1 cm, low-risk carcinomas in some patients [34]. Radioiodine ablation is recommended for patients with known residual tumor and probably also for those at high risk of recurrence. Some

patients with anaplastic thyroid cancer will respond to combined radiation and chemotherapy after thyroidectomy [5].

Thyroid Disease During Pregnancy

Both hypothyroidism and hyperthyroidism can complicate pregnancy (see ▶ Chap. 12, "Medical Problems During Pregnancy"). Hypothyroidism causes anovulation and rarely coincides with pregnancy. When hypothyroidism occurs, it is associated with gestational hypertension, premature labor, and low birth weight. Monitoring and management of the pregnant patient with thyroid disease requires the use of trimester-specific reference ranges for TSH and serum free T4 [39].

Thyroid-binding globulin increases during pregnancy, and so total T_3 and T_4 increase as well. Her dose of L-thyroxine should be adjusted to maintain the TSH level in the normal range on a sensitive assay [39]. In general, the pregnant patient with prepregnancy hypothyroidism will require an increase in her L-thyroxine of about 30 %. A convenient way to increase her L-thyroxine dose is for her to take nine doses per week rather than seven. Her TSH should be monitored 4 weeks after a dosage change and every 4 weeks during the first half of her pregnancy. The TSH should be rechecked at least once between 26 and 32 weeks gestation. After delivery, the patient should resume her prepregnancy dose and have her TSH assessed 6 weeks postpartum [39].

Hyperthyroidism during pregnancy is relatively uncommon and caused by the same etiologies as in nonpregnant patients, with Graves' disease being the most common cause. Thyrotoxicosis may lead to spontaneous abortion, stillbirth, neonatal death, and low birth weight [39]. All patients with a suppressed TSH should have their serum free T4 determined. Antithyroid drugs, usually propylthiouracil during the 1st trimester, followed by methimazole during the 2nd and 3rd trimester are recommended for treatment in pregnant patients. In addition, propranolol and occasionally thyroid resection may be used for treatment [39]. Any use of radioactive iodine is contraindicated during pregnancy.

Postpartum thyroiditis is a transient autoimmune thyroid dysfunction that occurs within the first postpartum year (see ▶ Chap. 15, "Postpartum Care"). It is probably an exacerbation of a preexisting subclinical autoimmune thyroiditis [5, 40]. The true incidence is 5–10 %, although it is frequently underdiagnosed [37]. The most common complaints are depression, poor memory, and impaired concentration. The clinical course consists of a hyperthyroid phase (which may be absent), followed by a hypothyroid phase and eventually a return to euthyroid status. The diagnosis is usually made with a TSH measurement. Patients with antibodies to thyroid peroxidase and thyroglobulin are at increased risk of developing this syndrome [41]. Patients who have one episode of postpartum thyroiditis are at increased risk for recurrence with future pregnancies and may develop permanent hypothyroidism [40].

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