Introduction

Knowledge of benign thyroid disease is important for the otolaryngologist head and neck surgeon as thyroid surgery accounts for a major portion of all operations performed in the head and neck region. Although most of these surgeries are indicated to treat malignant or potentially malignant tumors, surgical indications exist for treatment of many benign diseases of the thyroid. Benign diseases of the thyroid are quite common and affect women more frequently than men by a ratio of 5 to 1. The prevalence of thyroid nodules determined by ultrasound or autopsy is 30 to 50 percent; only five percent of these are malignant. Benign thyroid disease will be evaluated by the head and neck surgeon for a variety of reasons including: compressive symptoms, differentiation from malignant disease, cosmetic deformity, and failure of medical management of thyroid disease. Benign thyroid disease can be divided into benign nontoxic, benign toxic and inflammatory conditions. This paper will review nontoxic diffuse goiter, toxic multinodular goiter, thyroid adenoma, toxic diffuse goiter (Graves’ disease), chronic thyroiditis (Hashimoto’s), subacute thyroiditis (De Quervain’s), and Riedel’s thyroiditis.

Anatomy and Physiology

The thyroid gland is composed of 2 encapsulated lobes, one on either side of the trachea, connected by a thin isthmus that crosses the trachea anteriorly just below the cricoid cartilage. Occasionally, a pyramidal lobe is found extending superiorly from the isthmus in the midline. Embryologically, the thyroid develops as a thickening in the pharyngeal floor that elongates inferiorly as the thyroglossal duct and divides into 2 lobes as it descends through the neck. Congenital thyroid anomalies include: failure of one or both thyroid lobes to develop (agenesis or hemiagenesis), thyroid remaining at the base of tongue (lingual thyroid), thyroid tissue found at other locations between the base of tongue and lower neck (thyroglossal duct remnant), and substernal thyroid. In the case of a substernal thyroid, the thyroid follows the developmental path of the heart into the thorax where it may later manifest as a substernal goiter with compression of
the trachea, recurrent laryngeal nerve, or even the superior vena cava. Blood supply of the thyroid is via the superior and inferior thyroid arteries; venous drainage is more variable but usually there are paired superior, middle, and inferior thyroid veins.

Histologically, thyroid tissue is composed of spherical thyroid follicles. Each follicle consists of a single layer of cuboidal follicular cells surrounding a lumen filled with a homogenous material called colloid. With stimulation, the follicular cells become columnar and the follicles are depleted of colloid; with suppression, the follicular cells become flat and colloid accumulates. The thyroid also contains parafollicular C cells which produce calcitonin.

**Thyroid Hormone Synthesis and Secretion**

Synthesis of T4 and T3 by the thyroid gland involves 6 major steps: active transport of iodide across the basement membrane into the thyroid follicular cell (iodide trapping), oxidation of iodide and iodination of tyrosyl residues in thyroglobulin, coupling of iodotyrosine molecules within thyroglobulin to form T3 and T4, proteolysis of thyroglobulin with release of free iodotyrosines and iodothyronine, deiodination of iodotyrosines within the follicular cell with conservation and reuse of the liberated iodide, and, under certain circumstances, intrathyroidal deiodination of T4 to T3.

The T3 and T4 released from the thyroid by proteolysis reach the bloodstream where they are bound to thyroid hormone binding proteins. The major thyroid hormone binding protein is thyroxine binding globulin (TBG) which normally accounts for 75% of the bound hormone. All of the circulating T4 is produced by the thyroid; whereas, 20% of T3 is produced by the thyroid and the rest is produced by peripheral deiodination of T4 at extrathyroidal sites. T3 is by far the most active thyroid hormone. Peripheral deiodination of T4 can also result in reverse T3, a largely inactive thyroid hormone.

All reactions necessary for the production of T3 and T4 are positively influenced by thyroid stimulating hormone (TSH). Pituitary TSH secretion is controlled by a negative feedback mechanism modulated by the circulating levels of free T4 and free T3. Increased levels of free T4 and free T3 inhibit release of TSH and decreased levels of free T4 and free T3 stimulate release of TSH. Thyrotropin releasing hormone (TRH), synthesized by the hypothalamus also influences the secretion of TSH. When TRH is released into the portal system between the hypothalamus and pituitary, it causes release of TSH from anterior pituitary thyrotropic cells. The precise regulation of TRH synthesis and release has not been completely elucidated although T4 and T3 play a role.

An adequate supply of iodine is essential to normal levels of thyroid hormone production. The recommended minimum intake of iodine is 150 micrograms a day; intake of less than 50 micrograms a day is associated with goiter. High iodine levels inhibit iodide oxidation and organification; iodine excess inhibits thyroglobulin proteolysis (this is the principal mechanism for the antithyroid effect of inorganic iodine in patients with thyrotoxicosis).
Effects of Thyroid Hormones

1. Fetal brain development and skeletal maturation are dependent on fetal thyroid hormone production. In the absence of fetal thyroid hormone secretion, cretinism results (mental retardation and dwarfism).

2. T3 increases oxygen consumption and heat production which contributes to increased basal metabolic rate and the increased sensitivity to heat in hyperthyroidism and increased sensitivity to cold in hypothyroidism.

3. T3 stimulates transcription of myosin heavy chain alpha and inhibits transcription of myosin heavy chain beta, improving cardiac muscle contractility. T3 also increases transcription of calcium ATPase in the sarcoplasmic reticulum, alters isoforms of sodium-potassium ATPase genes, and increases beta-adrenergic receptors and the concentration of G proteins. Thus, thyroid hormones have significant positive inotropic and chronotropic effects on the heart.

4. Thyroid hormones increase the number of beta-adrenergic receptors in heart muscle, skeletal muscle, adipose tissue, and lymphocytes. Sensitivity to catecholamines is markedly increased in hyperthyroidism and treatment with beta-blockers may be helpful in controlling tachycardia and arrhythmias.

5. Thyroid hormone stimulates gut motility which can result in diarrhea in hyperthyroid states and constipation in hypothyroidism.

6. Thyroid hormone increases bone turnover. Bone resorption is increased more than bone formation which may result in significant osteopenia in chronic hyperthyroidism.

7. Thyroid hormone stimulates hepatic gluconeogenesis and glycogenolysis as well as intestinal absorption of glucose. This results in increased serum glucose. Thyroid hormone also causes increased cholesterol synthesis and degradation as well as increased lipolysis. This results in a lowering of serum cholesterol.

Diffuse and Multinodular Goiter

Multinodular goiter is one of the most common endocrine diseases worldwide, affecting 500-600 million people. Multinodular goiter is more prevalent in areas where iodine is lacking in the diet. In iodine deficient areas, hypothyroidism results with an increase in TSH. Increasing TSH causes growth of the thyroid gland and the development of diffuse nontoxic goiter. With growth of the thyroid gland, thyroid function often becomes autonomous, that is, thyroid hormone secretion becomes independent of TSH secretion. Multinodular goiters evolve from diffuse goiters. One or more follicles will have greater intrinsic growth and functional capability and continue to grow and function despite declining TSH secretion causing first a nontoxic multinodular goiter and ultimately a toxic multinodular goiter. Though usually associated with iodine deficiency, multinodular goiter also occurs in populations whose diets are iodine replete; this suggests other factors such as genetic influences may play a role in development of
multinodular goiter. A gene located on chromosome 14q, MNG-1, has been associated with familial nontoxic multinodular goiter and polymorphism of codon 727 has been associated with toxic multinodular goiter.

Most commonly, the patient with multinodular goiter is unaware of any problem until the diagnosis is made during a routine physical exam or evaluation for another problem. Patients with longstanding multinodular goiter are more likely to develop clinical or subclinical thyrotoxicosis. Patients may be referred to the otolaryngologist for compressive symptoms or suspicion of malignancy. Symptoms of tracheal compression include dyspnea, stridor, cough and choking sensations. Initially mild tracheal compression is asymptomatic. When tracheal compression becomes more significant, dyspnea and stridor develop. In those patients with a substantial intrathoracic component to their goiter, dyspnea and stridor may be nocturnal or positional, occurring primarily during maneuvers that force the thyroid into the thoracic inlet such as reaching. Compression of the jugular or subclavian veins or superior vena cava results in facial plethora and dilated neck veins. Pemberton’s maneuver, elevation of both arms until they touch both sides of the head for one minute, may demonstrate congestion, cyanosis or facial discomfort. Vocal cord paralysis, usually transient, can occur secondary to stretching or compression of one or both recurrent laryngeal nerves. Rapid, painful growth of a nodule may represent hemorrhage into a degenerating colloid nodule; if this occurs in an intrathoracic nodule, acute airway obstruction may occur. FNA may be indicated in patients with fast-growing or dominant nodules and nodules with a firmer consistency than other nodules within the same gland.

Workup includes laboratory studies such as TSH, T4 and T3 to determine the functional status of the thyroid. Diffuse or nodular goiter may be investigated with pulmonary function tests if tracheal compression is suspected; flow-volume loop tracings may be abnormal even in patients who are asymptomatic. CT and MRI are highly sensitive methods for detecting tracheal compression or intrathoracic extension of a goiter. If administration of iodinated contrast is necessary, pretreatment with antithyroid drugs may be recommended to avoid acute thyrotoxicosis.

Grossly, the thyroid gland in multinodular goiter consists of nodules that vary in size and shape. Histologically, multinodular goiters contain follicles of various sizes lined by cuboidal or flat epithelium; foci of hemorrhage and chronic inflammation are present. Larger nodules can develop pseudocapsules that usually incompletely encapsulate and merge into surrounding stroma.

Suppression therapy is the administration of thyroid hormone in order to suppress TSH and decrease the size of the goiter. This therapy has met with variable success and includes a risk of inducing thyrotoxicosis if the thyroid nodularity has been functioning independently. The efficacy of this approach is controversial. One study showed a mean 25% decrease in size of goiter at 4 months; although, when treatment was discontinued, thyroid size returned to baseline. Best results are obtained with small goiters. Suppression is associated with a risk of cardiac arrhythmias and osteopenia if the suppression is prolonged. These risks are greatest in the elderly population.
Medical treatments may also include antithyroid drugs such as propylthiouracil and methimazole. These drugs can normalize thyroid hormone levels in patients with toxic multinodular goiter. Long term treatment is considered safe. Side effects of antithyroid drugs include rash (5%) and agranulocytosis (0.5%). Rash can usually be managed with antihistamines and does not require cessation of therapy. Agranulocytosis is a serious side effect which is often heralded by a fever and sore throat. It requires cessation of therapy, appropriate antibiotic therapy, and shifting to an alternative therapy.

Radioiodine (I-131) is another treatment option for patients with both toxic and nontoxic multinodular goiter. It can reduce the size of the goiter and decrease the presence of hyperthyroidism. This treatment modality has been shown to reduce the size of toxic and nontoxic multinodular goiter by approximately 40-60% in 2 years. Return to euthyroid state is dose dependent and in one study 88% of patients treated were euthyroid at 5.2 years follow up. Disadvantages of I-131 include the possible need for more than one treatment, delayed effects, risk of hypothyroidism or the development of Graves’ disease, and it is contraindicated in pregnant women or women who want to become pregnant in the next year.

Surgical therapy for nontoxic goiter may be necessary in extremely large goiter, suspicion of malignancy, tracheal or esophageal symptomatology, substernal extension, vocal cord paresis, or rapid growth. Nontoxic multinodular goiter can be treated with either total thyroidectomy or subtotal thyroidectomy; this will provide pathologic confirmation, avoidance of radiation, one-stage treatment and low risk of recurrence. Toxic multinodular goiter is commonly treated with subtotal or total thyroidectomy.

Prior to treatment with radioactive iodine or surgical treatment, patients with toxic multinodular goiter need pretreatment cardiac evaluation and medical management as indicated. This will often include the need for antithyroid medications, beta-blockers, and potassium iodide. If possible, it is recommended to treat the patient until he is euthyroid and any cardiac problems are well controlled. When nonsurgical treatment options are selected, it is recommended that patients undergo serial examinations with thyroid laboratory evaluation and ultrasound as needed to identify any enlarging or dominant nodules that pose a risk of malignancy.

**Graves’ Disease**

Graves’ disease is the most common form of thyrotoxicosis. This syndrome consists of one or more of the following features: thyrotoxicosis, goiter, ophthalmopathy, dermopathy. It has an autoimmune etiology and a strong familial predisposition; approximately 15% of patients with Graves’ disease have a close relative with the disorder and approximately 50% of relatives of patients with Graves’ disease have circulating thyroid autoantibodies. Females are diagnosed with Graves’ disease five times more often than males; the peak age at diagnosis is 20 to 40 years of age. In Graves’ disease, T lymphocytes become sensitized to thyroid antigens and stimulate B lymphocytes to synthesize antibodies to these antigens. Thyroid autoantibodies, TgAB and TPO Ab, are found in both Hashimoto’s and Graves’ disease; TSH-Rab[stim] is unique to Graves’ disease. This autoantibody binds to the TSH receptor and stimulates the gland into hyperfunction. Triggers to acute episodes of Graves’ disease include: pregnancy and the postpartum period, iodine excess, lithium therapy, viral or bacterial infections and glucocorticoid withdrawal.
In young patients first presenting with Graves’ disease, symptoms are those of thyrotoxicosis including: palpitations, nervousness, easy fatigability, diarrhea, excessive sweating, intolerance to heat and preference for cold. There can be marked weight loss in the face of hyperphagia. Thyroid enlargement, eye signs and mild tachycardia may be present. In older patients, the clinical picture usually includes cardiovascular and myopathic manifestations; commonly, the patients complain of palpitations, dyspnea on exertion, tremor, nervousness and weight loss.

The development of Graves’ ophthalmopathy may involve cytotoxic lymphocytes sensitized to a common antigen such as TSH-R found in orbital fibroblasts, orbital muscle and thyroid tissue. Graves’ ophthalmopathy involves orbital myositis with swollen orbital muscles, proptosis of the globes and diplopia as well as redness, and periorbital edema. The American Thyroid Association has set forth a classification of eye signs. Class one involves spasm of the upper lids associated with active thyrotoxicosis; class two is characterized by soft tissue involvement with periorbital edema and chemosis; class three is proptosis as measured by Hertel exophthalmometer; class four is extraocular muscle involvement, most commonly the inferior rectus which limits upward gaze; class five is characterized by corneal involvement; class six is loss of vision due to optic nerve involvement.

Grossly, the thyroid gland is symmetrically enlarged. Histology of the thyroid gland reveals follicles lined with tall columnar cells with basally located nuclei. Colloid adjacent to epithelium appears vacuolated and scalloped. Some follicles contain almost no colloid. The stroma contains lymphocytes. The follicular epithelium often projects into the lumen of the follicles the form of small papillary infoldings.

Treatment of Graves’ disease may involve antithyroid drugs, surgery or radioactive iodine. Graves’ disease can be treated with antithyroid drugs such and propylthiouracil and methimazole. The duration of therapy is quite variable and can range from 6 months to 20 years or more. Remission may occur in 20-40% of patients treated for 6 months to 15 years; incidence of relapse is as high as 50-60%.

I-131 is an option for treating patients with Graves’ disease. This radioactive iodine is an excellent method for destroying overactive thyroid tissue. Rates of subsequent thyroid cancer, leukemia or other malignancies have not been shown to be increased in patients treated with I-131, and children born to parents previously treated with radioactive iodine show normal rates of congenital abnormalities. Radioactive iodine is absolutely contraindicated in pregnant women as radiation is harmful to the developing fetus. Following I-131 therapy, ophthalmopathy worsens or appears in a significant proportion of patients; this can be controlled with three months of treatment with prednisone post-radiation.

Surgical treatment consists of subtotal or total thyroidectomy. This is usually offered to patients with very large or symptomatic goiters, those who cannot tolerate or do not respond well to drug therapy, and those with severe or progressive ophthalmopathy. Prior to surgery, an attempt is made to bring the patient to a euthyroid state. Also, potassium iodide can be given two weeks prior to surgery to diminish vascularity of the gland and simplify surgery.
Complications of Graves’ disease include acute thyrotoxicosis and thyroid crisis (thyroid storm). Acute thyrotoxicosis may be managed with beta-blockers such as propranolol to control tachycardia, hypertension and atrial fibrillation. Barbiturates such as phenobarbital accelerate T4 metabolism and may be helpful for its sedative effect and to lower T4 levels. Cholestyramine will lower serum T4 by binding it in the gut. Thyroid storm is an extreme form of thyrotoxicosis which is relatively rare today. Patients present with delirium, severe tachycardia, vomiting, diarrhea, dehydration, and high fever. The mortality rate is high.

**Toxic Adenoma**

An autonomously functioning thyroid nodule that hypersecretes T4 and T3 is called a toxic adenoma. This can lead to clinical or subclinical thyrotoxicosis. The etiology of toxic adenoma is related to iodine deficiency as comparison of rates of development of toxic adenoma between populations in which dietary iodine is relatively replete versus relatively lacking show higher rates of toxic adenomas in populations that have lower dietary iodine. Commonly, the patient is an individual over 40 who has noticed the growth of a longstanding thyroid nodule. Women are diagnosed with toxic adenoma six times more often than men. Symptoms of hyperthyroidism may be noted. The natural history of toxic adenoma has been extensively studied; a German study of 375 euthyroid patients with toxic adenoma followed for 17 years showed 18% became hyperthyroid. Tendency to become hyperthyroid is age related with younger patients having a lower chance and older patients having a higher chance of becoming hyperthyroid. Nodules that produce thyrotoxicosis are virtually always greater than 3 cm in diameter. Laboratory studies show suppressed TSH and marked elevation of T3 levels, often with only borderline elevation of T4. Toxic adenomas are almost never malignant. They can usually be managed by antithyroid drugs; however, these medications do not inhibit the proliferative effects of the cellular defect. Thus, the nodule will usually continue to increase in size and more definitive therapy such as I-131 or unilateral lobectomy may be pursued.

**Chronic Thyroiditis**

Chronic thyroiditis (aka Hashimoto’s thyroiditis or lymphocytic thyroiditis) is likely the most common cause of hypothyroidism and goiter in the United States. Chronic thyroiditis is thought to result from lymphocytes becoming sensitized to thyroidal antigens; autoantibodies are formed which react to these antigens. Autoantibodies include thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb) formerly called microsomal antibody, and TSH receptor blocking antibody (TSH-Rab[block]). During the early phase of chronic thyroiditis, TgAb is markedly elevated. Later, TgAb may disappear, but TPOAb may be detectable for many years.

The gland is heavily infiltrated with lymphocytes destroying normal thyroid architecture. Lymphoid follicles and germinal centers may be present. Follicular epithelial cells are frequently enlarged and contain basophilic cytoplasm (Hurthle cells). Destruction of thyroid parenchyma results in a fall in serum T3 and T4 and a rise is TSH. Increases in TSH may maintain adequate hormone synthesis by the development of thyroid parenchyma hypertrophy; occasionally, the gland fails and permanent hypothyroidism with or without goiter results.
Chronic thyroiditis may present as a goiter in a euthyroid patient or a patient with mild hypothyroidism. Gender distribution is four females to one male. As the process of thyroid destruction and enlargement is painless, patients may be unaware of the goiter unless it becomes very large. Where only 10-15% of young patients presenting with chronic thyroiditis develop permanent hypothyroidism, older patients with chronic thyroiditis have a much higher incidence of permanent hypothyroidism. Therapy with levothyroxine will cause regression of the goiter and treat the hypothyroidism. Occasionally, patients with chronic thyroiditis will have periods of thyrotoxicosis when large amounts of T3 and T4 are released as gland parenchyma is destroyed.

Subacute Thyroiditis

Subacute thyroiditis (also known as De Quervain’s thyroiditis) is the most common cause of thyroid pain and tenderness. It is an acute inflammatory disorder of the thyroid gland most likely due to viral infection. Suspected viral agents include mumps virus, cockssackie virus, and adenovirus. It usually affects patients in the 4th and 5th decades with a female to male ratio of 5 to 1. The incidence of subacute thyroiditis tends to be seasonal and geographic, coinciding with seasonal enterovirus infections. Histologic evaluation reveals destruction of thyroid parenchyma and the presence of many large phagocytic cells, including giant cells and granulomatous changes. Microabscesses and fibrosis may also be present. These changes revert to normal or minimal fibrosis when the disease subsides.

Patients with subacute thyroiditis present with fever, malaise, and soreness in the neck which may extend to the angle of the mandible or toward the ear lobes on one or both sides of the neck. The thyroid can be slightly to moderately enlarged; this enlargement is usually diffuse with the thyroid being firm in consistency but occasionally being quite hard. Initial features may be those of hyperthyroidism including palpitations, agitation and sweats. Unlike Graves’ disease, there is no ophthalmopathy. The thyroid gland is tender to palpation, sometimes exquisitely so. Laboratory studies during the initial phase of the illness will show elevations of T3 and T4 with suppression of TSH. Radioactive iodine uptake will be decreased and there will be an elevation in serum thyroglobulin. Thyrotoxicosis in subacute thyroiditis is the result of tissue injury followed by the release of large amounts of thyroid hormone into the circulation. ESR may be as high as 100 mm/h. Usually, thyroid autoantibodies are not present.

As the disease progresses and the patient begins to show signs of hypothyroidism, T4 and T3 will drop and TSH will rise. Thus, patients with subacute thyroiditis usually have a transient period of hypothyroidism. Subacute thyroiditis usually remits spontaneously over weeks to months. Relapses may occur when the T4 levels have fallen, TSH has risen and the gland is starting to recover function. Uncommonly, the course may extend over several years, with repeated bouts of inflammatory disease. Treatment is usually symptomatic and may consist of a course of NSAIDS or a glucocorticoid such as prednisone if pain, fever and malaise are disabling. Beta-blockers may be used if signs and symptoms of thyrotoxicosis are severe. Antithyroid drugs have no role because thyroid hormone biosynthesis is already low. Levothyroxine is indicated during the hypothyroid phase in order to prevent exacerbation of the disease induced by rising TSH levels. Permanent hypothyroidism results in approximately 5-10% of cases.
Other causes of anterior neck pain must be differentiated from subacute thyroiditis. These causes include hemorrhage into a thyroid nodule or cyst and acute suppurative thyroiditis. In both cases, radioactive iodine uptake studies show normal function of the unaffected areas of the gland. In acute suppurative thyroiditis, patients have greater leukocytosis, higher fever, more inflammation of surrounding tissues and a septic focus elsewhere in the body is usually evident.

**Riedel’s Thyroiditis**

Riedel’s thyroiditis is a rare disorder in which fibrous tissue replaces thyroid tissue. This disease usually occurs in middle-aged women and has a likely autoimmune etiology. Signs and symptoms of Riedel’s thyroiditis include the development of a rapidly enlarging, hard neck mass which may be associated with tracheoesophageal compression, suggesting the possibility of poorly differentiated thyroid cancer or thyroid lymphoma. Riedel’s thyroiditis is associated with other fibrosclerotic conditions such as retroperitoneal fibrosis and sclerosing cholangitis. In fact, within ten years of diagnosis, approximately 30% of patients develop retroperitoneal or mediastinal fibrosis. FNA or open biopsy may be needed to differentiate this entity from cancer. Treatment is focused on relief of obstruction and, to that effect, surgery may be necessary to relieve tracheal compression. Medical treatment with glucocorticoids and, more recently, tamoxifen has been employed with some success. Patients are initially euthyroid but later develop hypothyroidism as glandular tissue is replaced by fibrosis.

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