

TITLE: Benign Thyroid Disease

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RESIDENT PHYSICIAN: Naren Venkatesan M.D

FACULTY PHYSICIAN: Susan McCammon M.D.

SERIES EDITOR: Francis B. Quinn, Jr., M.D.

ARCHIVIST: Melinda Stoner Quinn, MSICS

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Introduction

Knowledge of the thyroid gland is integral to the field of Otolaryngology. This knowledge includes an understanding of embryology, anatomy, physiology in addition to pathology. With respect to pathology, the topics of thyroiditis, Graves disease, Goiters, and Nodules will be discussed. To begin, a short review of thyroid history will be presented.

History

The first knowledge of the thyroid gland comes from early 2700 BC in China. There, Emperor Shen Nung's prescriptions mention the use of seaweed for the treatment of goiter. Seaweed is known to be rich in Iodine. By 300 BC, the Ayur Veda, one of the Hindu holy texts, discusses goiters. From this date onwards, goiters are mentioned throughout several cultures progressing from Asia throughout Europe and Africa.

Moving forward several hundreds of year, another important leap forward occurred in 961. Abul Kasim, a personal physician to Caliph El-Hakin III of Cordoba, first describes performing a thyroidectomy for goiter as well as how to perform a needle biopsy of the thyroid. Progressing forward still to Renaissance times, in 1500, Leonardo da Vinci is first person to recognize and draw the thryoid gland in its full anatomy. Finally, in 1656, Thomas Wharton names gland "thyroid" after the shape of an ancient Greek shield. The symbolic shields were those that had the depression in the middle with the edges raised, similar to the lobes and the isthmus.

From this point, taking a step forward to the 1800s, more recent discoveries began to occur with regards to the thyroid. In 1820, Jean Francois Coindet concluded that Iodine deficiency causes goiter and began treatment of goiter with Iodine. At that time, much of

the world had access to Iodine but did not realize this correlation. Further, while some genetic component is noted with regards to goiter, the predominant cause is dietary insufficiency of Iodine. Next, in 1829, Lugol recommends use of aqueous solution of Iodine made from KI to treat goiter. In 1902, F. de Quervain describes subacute granulomatous thyroiditis which will eventually be renamed in his honor.

In 1905, Robert Abbe treats Graves disease by implanting radium into the patient's goiter, an early, ingenious predecessor to radioactive iodine treatment. Then, after a decade of research and work on the gland, Kocher received the Nobel Prize for his work on Thyroid Physiology, Pathology, and Surgery in 1909. From that time until now, much work has been performed on the Thyroid gland giving us many new advances in understanding and treating the diseases. Two notable advances should be mentioned here. First, in 1954, J. Gross and R. Pitt-Rivers isolate and synthesize T₃. This would eventually lead to manufacturing of Levothyroxine which would revolutionize the treatment of hypothyroid patients. Last, in 1970, A. Schally identifies TRH and receives Noble Prize for this work in 1977. This knowledge was fundamental as it linked the Thyroid gland to the other Endocrine organs as having the traditional hypothalamus-pituitary-End Organ axis and established the understanding of negative feedback.

Embryology

The thyroid gland is derived from two predominant cell lines – endoderm and neural crest cells. The endoderm cells begin in the region of the head and migrate caudally to the eventual location of the thyroid in the neck. These cells proliferate and become follicular cells. The neural crest cells combine with the 4th and 5th branchial pouches and form the Parafollicular C-Cells and the parathyroids.

Because of the descent of the endoderm cells, a tract forms which connects to the tongue. The tract is the foramen cecum and is usually obliterated as the fetus develops. However, if it is persistent, it can lead to formation of a thyroglossal duct cyst. This presents as a midline-cystic mass that is usually larger than 1 cm and moves as the patient swallows. Treatment of the thyroglossal duct cyst involves first evaluating the cyst with appropriate imaging. The key is to evaluate if the patient has thyroid tissue, which lies in the cyst. There are two main concerns here. First, some patients only thyroid tissue may lie within the cyst. While the cyst should still be removed, this fact should be known so that thyroid hormone replacement can be started. Second, in 1% of thyroglossal duct cysts, carcinoma may be present. It is important as about 1/3 of these patients may have a malignancy in the rest of their thyroid tissue. The surgery to cure these patients is the Sistrunk procedure with the integral step of removing the mid-portion of the hyoid bone to prevent recurrence.

Anatomy

A thorough knowledge of anatomy is integral in treatment of thyroid diseases. As a brief overview, the blood supply to the thyroid is through the superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the

thyrocervical trunk. Sometimes, further blood supply may be provided by the thyroid ima artery to the thyroid isthmus.

Physiology

As integral as the anatomy is, an understanding of the physiology is more essential as this allows appropriate management. The thyroid gland functions similarly to the remainder of the endocrine glands. It functions through the hypothalamic-pituitary-thyroid axis. This axis works through the concept of negative feedback. The hypothalamus releases TRH, thyrotropin releasing hormone, which makes the anterior pituitary release TSH, thyroid stimulating hormone. In turn, TSH causes the thyroid to release thyroxine, T4, and triiodothyronin, T3. Peripherally, T4 is converted to T3 which is more active. Thyroid hormone has a negative feedback response on the anterior pituitary and hypothalamus. Of particular note, when TSH binds to the receptors on the Thyroid triggering organification, the attachment of iodine to stored thyroglobulin.

Thyroiditis

Now, we will discuss some of the pathology associated with the thyroid. Thyroiditis is a general term which includes any form of inflammation of the thyroid gland. Four of the most common types are Hashimoto's, Reidel's, de Quervain's, and Post-partum.

Hashimoto's thyroiditis is the most famous of this group of diseases. Dr. Hakaru Hashimoto first described it in 1912 in Germany. He described it by his findings as chronic lymphocytic thyroiditis. The chronic lymphocytic infiltrate is due to the invasion of T-cells and possibly B-cells. The disease occurs secondary to antibodies to either thyroid peroxidase or thyroglobulin or both. Histologically, it begins with rare germinal centers which eventually turn into multiple mature germinal centers. This is also the reason why these patients are at an increased risk of lymphomas, usually non-Hodgkin's lymphoma.

Typical presentation of a patient with Hashimoto's disease is a young to middle-aged woman with a firm, diffuse, bilateral goiter. As an autoimmune disease, it is much more common in women and often associated with other autoimmune diseases. It also has a strong family history and has genetic components, with the genes HLA-DR5 and CTLA-4 being implicated. These patients, while typically hypothyroid, can present as euthyroid or even in the middle of an episodic bouts of hyperthyroidism. Some of the typical symptoms that a patient in the hypothyroid state would present with are weight gain, depression, bipolar disorder, cold sensitivity, fatigue, bradycardia, infertility and menorrhagia, muscle weakness, and hair loss. While the clinical presentation may be classic, it is still important to confirm the diagnosis. First, order a TSH, free T4, and T3 levels. If the TSH levels are low, check for auto-antibodies to thyroglobulin or thyroid peroxidase. Also, an FNA is often recommended as the patient's goiter may be sign of another thyroid disease. After confirming the diagnosis, treatment consists of levothyroxine for the hypothyroidism as well as frequent monitoring of the thyroid by physical exam. An ultrasound is also recommended if at any point a nodule is noted. Due

to the increased risk of thyroid lymphoma, any nodule is concerning, and a thyroidectomy is advocated.

Another form of thyroiditis is Reidel's thyroiditis. It usually presents in middle-age women as a painless, firm nodule with normal thyroid function. The disease is characterized by extensive fibrosis and fixation of the thyroid to adjacent structures that can cause compression of trachea or the esophagus or both. The fibrosis can even be present in other areas of the body, such as retroperitoneal fibrosis and sclerosing cholangitis. As it is a nodule, the first recommendation would be to perform an FNA biopsy; however, the extensive fibrosis often prevents an appropriate read. Therefore, the recommendation is, in a patient with compressive symptoms, to perform a thyroidectomy or at least excise the isthmus to separate the lobes and release the pressure.

The next form of thyroiditis is de Quervain's thyroiditis, which is also known as subacute thyroiditis. A typical case is a young adult, often a female, with a recent history of an upper respiratory illness that presents with an exquisitely tender thyroid gland upon palpation. These patients should be counseled that this form of thyroiditis usually resolves on its own within weeks to months. These patients however require monitoring as they will experience an episode of hyperthyroidism, hypothyroidism, or both.

Another form of thyroiditis is Post-Partum thyroiditis. As the name states, it usually occurs shortly after delivery. It also presents with phases of either hypothyroidism or hyperthyroidism much like subacute thyroiditis. Again, similar to subacute thyroiditis, these patients usually return to euthyroid function after 12-18 months; however, about 20% of patients remain hypothyroid. This disease has also been linked to autoimmune diseases, and females with other autoimmune diseases are at an increased susceptibility for this disease.

Graves Disease

Graves disease is typified as the autoimmune disorder which causes hyperthyroidism. It is a disease usually seen in females who have an antibody towards the TSH receptor on the thyroid. The antibody then functions like TSH causing release of T4 and T3; however, as it is secondary to the antibody, there is no negative feedback. Therefore, there is unregulated release of thyroid hormone as well as hypertrophy of the thyroid gland, forming a goiter. Graves disease is the most common cause of hyperthyroidism in children and adolescents with a female predilection, anywhere from 5:1 to 10:1.

While patients will present with signs of hyperthyroidism, three key findings define patients with Graves. These are goiter along with ophthalmopathy and pretibial myxedema. Graves ophthalmopathy is characterized by inflammation of the extraocular muscles, orbital fat, and connective tissue. This ophthalmopathy can lead to conjunctival or corneal irritation, burning, photophobia, tearing, pain, and sandy sensation in the eyes. Diplopia is often common due to the limitation of eye movement. Signs of hyperthyroidism can be weight loss, heat intolerance, warm/moist skin, fine tremor, hyperreflexia, increased fatigability, and cardiovascular changes, including hypertension, palpitations, and left ventricular hypertrophy. Appropriate treatment of Graves disease

involves the use of Beta-blockers to combat the autonomic hyperactivity and the use of Propylthiouracil or Methimazole to decrease the amount of thyroid hormone released. PTU is preferred as it not only works in decreasing the release of hormone but also prevents peripheral conversion from T4 to T3. Definitive treatment involves the use of either Radioactive Iodine (RAI) therapy or Thyroidectomy. RAI is clearly less-invasive but has the limitation of taking months to have a completed effect as the cellular uptake is variable. Contra-indications to RAI include pregnancy, findings of a nodule, or ophthalmopathy which may be worsened.

Goiter

Goiter is a non-specific term used for a swelling of the thyroid gland. It was first described and labeled as such in 1625 by English and Arabic scientists. They can be classified in 3 different categories: Toxic or non-toxic, diffuse or nodular, and solitary or multiple. The prevalence in the United States is around 4-7%. The WHO provides a system to grade goiters which roughly grades on the fact of is it present, palpable, and then visible which respectively increase the score from Grade 0 to Grade 3. Diffuse goiters are often associated with the thyroiditis or Graves. Multinodular goiter is the most common endocrine disorder affecting 500-600 million people worldwide, with the iodine deficiency being the most common trigger. Further testing shows that, in Iodine-deficient areas, increased TSH is leads to goiter formation. On the other hand, in more industrialized nations, genetics has been shown to a play a role noted by the MNG-1 gene on chromosome 14q and codon 727 found in affected patients.

Typical presentation of a patient with multinodular goiter is a patient with globus sensation, dysphagia, recumbent dyspnea, tracheal deviation, or hoarseness. If a patient also demonstrates a possibility that there is vocal fold paralysis or the thyroid is fixed to the trachea or esophagus, these findings are worrisome for cancer. The toxic form of multinodular goiter simply refers to the fact that in about 5-10% of patients they also have episodes of acute onset thyrotoxicosis. They may have low to normal TSH and even normal to high normal T4 and T3.

Of clinical importance, a goiter can also present with substernal extension. A patient with substernal goiter typically complains of cough, dyspnea, stridor, choking symptoms, and/or dysphagia. These goiters tend to be slow, progressive growing goiters which on CT scan may demonstrate compressive signs, including tracheal deviation. Substernal goiters are associated with a risk of cancer, measuring 1.3-3.7 new cases per 1000 patients. Current articles suggest that the diagnosis of a substernal goiter alone demands a thyroidectomy. This correlation is due to the fact that these goiters can not be closely followed. An ultrasound is difficult due to the bony landmarks in the area which provide interference, and FNA is likewise difficult to obtain a good sample due to the various structures which are often in the way.

Thyroid Nodules

As with every other thyroid disease, thyroid nodules are more prevalent in women than men, with the ratio reported as 5:1. With the findings of a nodule, the key objective

is rule out cancer. 5-15% of nodules are cancerous, and the incidence of cancer continues to increase. This change mirrors the increasing incidence of papillary thyroid cancer which was 3.6 per 100000 in 1973 and has risen to 8.7 in 100000 in 2002. This increase has mostly been attributed to increased testing and better radiographic studies which identify nodules that are smaller than 2 cm. A nodule is radiographically defined as a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma.

The first factor in a nodule is size, as the American Thyroid Association states that the cost-benefit of evaluating nodules less than 1 cm is futile. In addition to evaluating a nodule greater than 1 cm, it is imperative to perform a thorough history and physical. Important questions in a patient's history include radiation as a child, family history, rapid growth of the nodule, hoarseness, and if the nodule was found on PET scan as an incidentaloma. On physical exam, it is important to know if the vocal cords are paralyzed, if lateral cervical lymphadenopathy exists, or if the nodule is fixed to surrounding tissues.

The first step as with any thyroid gland change is to perform an ultrasound along with thyroid function studies. If the TSH is elevated, there is increased suspicion for a malignancy; however, if the TSH is low, a radionuclide thyroid scan is recommended. The radionuclide scan works by demonstrating the level of uptake of an iodine tracer. Areas with increased uptake are hot nodules and are rarely associated with cancer. Those nodules with decreased uptake are cold nodules and are suspicious for cancer. With regards to the ultrasound, several findings should be noted, including the exact nodule size, other nodules, any enlarged cervical lymph nodes, possible cystic component of the nodule, and the nodule's exact location within the thyroid. Any nodule, that is either greater than 50% cystic nature or located posteriorly, increases the difficulty in obtaining a successful FNA.

The next step then is to perform a fine needle aspiration biopsy. As a side note, it is of particular importance to perform an FNA on a nodule seen in a patient with Hashimoto's thyroiditis as they have an increased risk of malignancy. Four possible readings exist for an FNA biopsy are benign, malignant (given to a biopsy with greater than 95% risk), indeterminate, and non-diagnostic. In addition to these four readings, the National Cancer Institute has proposed two other categories – one for biopsies carrying greater than 75% risk and those of follicular lesions which are uncertain with regards to risk of malignancy. These two others are rarely used currently. Malignant characteristics on a FNA are nodule hypoechogenicity, increased intranodular vascularity, irregular infiltrative margins, microcalcifications, and an absent halo.

Four types of benign nodules exist. These are follicular adenoma, Hurthle cell adenoma, Hyalinizing trabecular adenoma, and nodular goiter. A follicular adenoma is a well-circumscribed, encapsulated lesion which occurs secondary to clonal growth. It often demonstrates degenerative changes such as hemorrhage, calcification, and fibrosis. The key on these nodules is to rule out capsular or vascular invasion which change the diagnosis to follicular cancer. Hurthle cell adenomas are also circumscribed and encapsulated lesions which show Hurthle cells (cells which are rich in mitochondria).

They appear much like follicular adenomas, and similarly, if there is any vascular or capsular invasion the diagnosis is changed to cancer. Hyalinizing trabecular adenoma is characterized by cells arranged in trabeculae, clusters, or both with highly granular cytoplasm. There is also extensive perivascular hyaline fibrosis. Last, there is nodular goiter which shows hyperplastic/dilated nodules of different sizes filled with colloid.

The American Thyroid Association releases further extensive information every few years. They also provide an excellent flow chart of the work-up of a patient with a nodule. Lastly, long-term management of a benign nodule is usually with ultrasound every 6 months for 3-5 years. If any changes occur, repeat FNA or provide option of thyroidectomy.

Conclusion

The importance of the thyroid gland cannot be underestimated as it plays a significant role in the daily treatment of patients. Also, a better understanding of the thyroid allows otolaryngologists to assess patients more appropriately and treat benign conditions as well as cancerous ones.

REFERENCES

- Hardy RG, Bliss RD, Lennard TW, Balasubramanian SP, Harrison BJ. Management of retrosternal goitres. *Ann R Coll Surg Engl.* 2009 Jan;91(1):8-11.
- Katlic MR, Wang C, Grillo HC. Substernal goiter. *Ann Thorac Surg.* 1985;39:391–9.
- Shai SE, Chen CY, Hsu CP, Hsia JY, Yang SS, Chuang CY, et al. Surgical management of substernal goiter. *J Formos Med Assoc.* 2000;99:827–32.
- Mack E. Management of patients with substernal goiters. *Surg Clin North Am.* 1995;75:377–94.
- Wax MK, Briant TDR. Management of substernal goitre. *J Otolaryngol.* 1992;21:165–70.
- Mackle T, Meaney J, Timon C. Tracheoesophageal compression associated with substernal goitre. Correlation of symptoms with cross-sectional imaging findings. *J Laryngol Otol.* 2007;121:358–61.
- Ben Nun A, Soudack M, Best LA. Retrosternal thyroid goiter: 15 years' experience. *Isr Med Assoc J.* 2006;8:106–9.
- Quadbeck B, Pruellage J, Roggenbuck U, Hirche H, Janssen OE, Mann K, et al. Long-term follow-up of thyroid nodule growth. *Exp Clin Endocrinol Diabetes.* 2002;110:348–54.
- Liel Y, Ariad S, Barchana M. Long-term follow-up of patients with initially benign thyroid fine-needle aspirations. *Thyroid.* 2001;11:775–8.
- Winbladh A, Jarhult J. Fate of the non-operated, non-toxic goitre in a defined population. *Br J Surg.* 2008;95:338–43.
- White ML, Doherty GM, Gauger PG. Evidence-based surgical management of substernal goiter. *World J Surg.* 2008;32:1285–300.
- Akbar SA, Ahmed N, Ali J, et al. Multinodular Goiter: frequency of malignancy and its histopathological types: A tertiary care hospital experience. *Professional Med J Mar* 2010;17(1): 40-43
- Cooper DS et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 2009; Vol 19 (11)
- Raffaelli et al. Surgical Treatment of Thyroid Diseases in Elderly Patients. *Am J Surg;* Volume 200 Issue 4 Oct 2010 467-472
- Day TA, Chu A, Hoang KG. Multinodular Goiter. *Otol Clin N Am* 2003. 36:35-54