

ENDOCRINE DISEASES

THYROID GLAND

Anatomy

The thyroid gland is a butterfly-shaped gland that sits in the lower part of the neck, at approximately the level of the second tracheal ring. It has left and right lobes connected by a narrow bridge of tissue, the isthmus. The sternohyoid and sternothyroid muscles lie anterior to the gland, and the trachea, larynx, and esophagus lie deep to it and on either side are the carotid arteries.

The adult thyroid gland weighs approximately twenty grams and is one of the most vascular organs in the body. The blood supply is derived from branches of the external carotid arteries, the superior thyroid arteries, and branches of the subclavian/thyrocervical trunk, the inferior thyroid arteries. Venous drainage occurs through the superior, middle, and inferior thyroid veins. The recurrent laryngeal nerves that supply sensory and motor innervation to the larynx run alongside the inferior thyroid arteries, in the posterior aspect of the lobes. The parathyroid glands, typically four, lie on the posterior aspect of the thyroid gland.

The gland is derived mainly from the endoderm. It appears at approximately 24 days post-conception, as a thickening on the floor of the pharynx at the site of the foramen cecum in the adult tongue. This endodermal thickening grows caudally, as the thyroglossal duct, into the neck, passing ventral to the embryonic hyoid bone and thyroid cartilage. The duct disappears by the 50th day of gestation but may persist anywhere along its migratory pathway as the pyramidal lobe of the thyroid, present in up to 50% of adults, or as a thyroglossal duct cyst. In addition, the ultimobranchial body, derived from the ectoderm, is the origin of the parafollicular C cells of the thyroid gland.

Physiology

The thyroid gland has two distinct groups of hormone-producing cells. Follicular cells produce, store, and release thyroxine (T4) and triiodothyronine (T3), major regulators of the basal metabolic rate. Parafollicular cells, or C cells, secrete calcitonin, a hormone that has a minor role in maintaining calcium homeostasis.

Follicular cells capture, actively import, and concentrate iodide from the circulation. The iodide is oxidized to iodine by the enzyme thyroid peroxidase (TPO). Thyroglobulin is a glycoprotein synthesized by the follicular cells and secreted into the extracellular storage space called the follicle. The tyrosine residues of thyroglobulin are iodinated forming mono- and di-iodotyrosine. This iodinated thyroglobulin is the storage form of the thyroid hormones within the follicle. When thyroid-stimulating hormone (TSH) stimulates the thyroid gland, the iodinated thyroglobulin is transported back into the follicular cell by endocytosis. It is then hydrolyzed to T3 and T4, the active forms of the hormone, and released into the circulation. Eighty percent of the circulating

ACS/ASE Medical Student Core Curriculum

Endocrine Diseases

hormone is T₄, but T₃, generated by the peripheral conversion of T₄ to T₃, is the most active form. Thyroglobulin itself is not released except under pathologic conditions.

Thyrotropin-releasing hormone (TRH), secreted by the hypothalamus into the hypothalamic–pituitary portal venous system, increases TSH release from the anterior pituitary. TSH stimulates the follicular cells to increase thyroglobulin synthesis, increase iodide transport efficiency, and stimulates the thyroid to release T₃ and T₄. Elevated concentrations of T₃ and T₄ provide negative feedback to TRH and TSH secretion.

The parafollicular C cells decrease serum calcium. They secrete calcitonin in response to high serum calcium, which inhibits osteoclast activity. Calcitonin secretion does not normally play a major role in regulating serum calcium levels. Its function probably is to protect the skeleton from excessive scavenging during times of high calcium demand such as growth, pregnancy, or lactation. The absence of calcitonin production after total thyroidectomy appears to have no demonstrable negative physiologic effect on calcium homeostasis.

Thyroid Nodules

Palpable thyroid nodules occur in about 4% of the United States population. At autopsy, thyroid nodules are noted in more than half of adults. Thyroid nodules are often detected by the patient themselves, by physical examination, or increasingly incidentally by radiographic tests done for some other indication. Only about 5% of thyroid nodules are malignant. However, due to the prevalence of thyroid nodules in the general population, appropriate evaluation is warranted to rule out carcinoma.

Evaluation begins with a thorough history and physical exam. History should include the duration of the nodule, any growth in size or change over time, and presence of symptoms. Compressive symptoms of neck pressure, dysphagia, dysphonia, dyspnea, or globus sensation may be present. Compressive symptoms may be exacerbated by lying supine or extending arms overhead. Symptoms can also be due to hyperthyroidism such as palpitations, heat intolerance, anxiety, or weight loss. A family history of thyroid malignancy or personal history of radiation exposure should be elicited.

The physical examination includes palpation of the entire thyroid gland and cervical lymph nodes. The thyroid should be examined with deglutition to assess for fixation to surrounding structures. Exam findings that may indicate malignancy include a firm fixed mass and cervical lymphadenopathy. Indirect or direct laryngoscopy is indicated when there is hoarseness.

The initial evaluation of a thyroid nodule includes measurement of serum TSH and a neck ultrasound, whether clinically palpable or incidentally noted. If the TSH is low, a thyroid uptake scintigram should be the next step to determine the etiology of hyperthyroidism. If the TSH is high or normal, the thyroid and cervical lymph nodes should be assessed by ultrasound. Ultrasound characteristics of thyroid nodules are used to determine whether they meet criteria

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

for fine needle aspiration biopsy (FNA). Thyroid nodules that do not require FNA are monitored with periodic ultrasound.

Ultrasound of the neck supplements PE findings. Ultrasound can determine the exact number and location of nodules, whether a nodule is cystic or solid, and detect enlarged or abnormal cervical lymph nodes. There are several ultrasound findings associated with a higher risk of cancer including hypoechogenicity, microcalcifications, irregular borders, internal vascularity, and taller than wide shape. These findings can help guide the selection of nodules for ultrasound guided FNA.

FNA cytology is the next step in the evaluation of a thyroid nodule based on size and imaging characteristics. FNA results fall under six major categories:

1. Non diagnostic – the smear does not have the adequate number of follicular cells necessary to make a cytologic diagnosis. Malignancy risk: 5-10%
2. Benign – usually colloid, adenomatous or hyperplastic nodule, autoimmune thyroiditis. Malignancy risk: 0-3%
3. Follicular lesion or atypia of undetermined significance (FLUS or AUS) – presence of atypical cells or mixed micro and macrofollicular features. Malignancy risk: 10-30%
4. Follicular neoplasm, suspicious for follicular neoplasm, or Hurthle cell neoplasm – microfollicular adenoma. Malignancy risk: 25-40%
5. Suspicious for malignancy – lesions have some features suggestive of, but not definitive for, papillary thyroid cancer. Malignancy risk: 50-75%
6. Malignant – this includes papillary thyroid cancer, medullary thyroid cancer, thyroid lymphoma, anaplastic cancer, and cancer metastatic to the thyroid gland. Malignancy risk: 97-99%

Cytologic results in categories 3 and 4 are described as indeterminate. The risk of malignancy indeterminate thyroid nodules is 10 to 40 percent. If a repeat biopsy confirms the indeterminate result, the FNA can be further evaluated by advanced molecular testing. There are three options available for molecular testing: mutational analysis, genomic sequencing, or combined mutation analysis with gene expression. Molecular tests have high negative predictive values to exclude malignancy. Thyroid lobectomy for diagnosis is an alternative to molecular testing and may be preferred for symptomatic nodules.

Medullary carcinoma is the only thyroid cancer that reliably expresses a tumor marker (calcitonin) measurable in the serum. Serum thyroglobulin levels may be elevated in follicular or papillary carcinomas, but are not reliable markers prior to thyroidectomy.

Management of thyroid nodules differs based on presence of compressive symptoms and biopsy results. Patients with nondiagnostic FNA should have a repeat ultrasound guided FNA biopsy. Patients with benign nodules causing lifestyle limiting symptoms or those with enlarging nodules on follow up ultrasound may benefit from thyroidectomy. Those with indeterminate biopsy results may have repeat FNA or elect for thyroid lobectomy for definitive diagnosis.

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

Molecular testing may avoid surgery if mutation analysis or genetic sequencing have benign characteristics. Patients with suspicious results of molecular testing on indeterminate thyroid nodules should proceed with thyroid lobectomy for diagnosis. For thyroid nodules with suspicious or malignant biopsy results, thyroidectomy should be performed. The decision for thyroid lobectomy or total thyroidectomy for suspicious or malignant nodules depends upon the size and location of nodules and the presence of high risk features such as extrathyroidal extension or lymphadenopathy.

In performing lobectomy or total thyroidectomy, great care is taken to preserve the parathyroid glands and their blood supply to avoid postoperative hypoparathyroidism and hypocalcemia. Injury to the recurrent laryngeal nerve leads to immobility of the ipsilateral vocal cord in the paramedian position causing hoarseness with a weak and breathy voice. If bilateral recurrent laryngeal nerves are injured both vocal cords become fixed in the paramedian position and a tracheostomy is required to maintain the airway. Injury to the external branch of the superior nerve results in loss of voice quality with deficits in high pitch and projection. Transient neurapraxia of the nerves is more common than permanent injury and usually resolves without sequelae. Bleeding into the operative bed can cause life threatening tracheal compression. If a postoperative hematoma occurs, the surgical wound should be opened, at the bedside if necessary, to avert an airway emergency.

Hyperthyroidism

Hyperthyroidism is a syndrome that is caused by excessive secretion of thyroid hormone. The lifetime risk of hyperthyroidism is approximately 5% for women and 1% for men. Graves' disease occurs predominantly in young women (8:1 ratio). Toxic nodular goiter is more common in older women. The most common cause is Graves' disease, or diffuse toxic goiter. Less commonly, hyperthyroidism is caused by a solitary toxic nodule or toxic multinodular goiter. TSH will be suppressed for each of these causes. Radionuclide thyroid uptake nuclear medicine imaging can differentiate these etiologies with diffuse increased uptake in Graves' disease, a solitary hot nodule, or multiple nodules with increased uptake.

Graves' Disease

Graves' disease is diffuse thyroid enlargement and hyperfunction from thyroid hormone receptor autoantibodies (TRAb), also referred to as thyroid stimulating immunoglobulins (TSI) with symptoms of hyperthyroidism: tremor, anxiety, palpitations, fatigue, heat intolerance, or weight loss. There may be ocular symptoms of exophthalmos, lid lag or retraction, proptosis, diplopia, deformity of the periorbital tissues with optic nerve involvement, and complete loss of vision. The pathogenesis of Graves' eye disease is due to expression of TSH receptors in the periorbital soft tissues leading to deposition of glycosaminoglycans.

There are three possible treatments for Graves' disease: antithyroid medications, radioiodine ablation, and thyroidectomy. All three modalities are effective and each has side effects. The choice of therapy is patient centered. The thionamides, methimazole and propylthiouracil,

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

interfere with the synthesis of thyroid hormones by inhibiting iodide organification and iodotyrosine coupling. They also reduce the rate of peripheral conversion of T4 to T3. Methimazole is more commonly used due to longer duration of action and fewer side effects, but is teratogenic. Propylthiouracil is preferred during the first trimester of pregnancy. Side effects of thionamides include hepatotoxicity and agranulocytosis. The beta blocker propranolol is used for initial symptom control in patients who experience tachycardia or palpitations. Following initial medical management, up to half of patients experience remission.

Radioiodine ablation (RAI) is a safe and effective treatment. It is administered as an oral formulation of I-131. Thyroid levels must be normalized with thionamides prior to RAI. Acute thyrotoxicosis or thyroid storm may occur following RAI, due to release of T3 and T4 from ablated follicular cells. Radioiodine ablation is contraindicated in pregnant or lactating women, those who desire immediate childbearing, or in patients with significant orbitopathy. The presence of thyroid nodules or compressive symptoms with Graves' disease are relative contraindications to RAI.

Total thyroidectomy provides rapid control of the disease and eliminates exposure to radioactivity, which some patients may prefer. Surgery is indicated in patients who are allergic to thionamides or have contraindications to RAI. Patients with severe hyperthyroidism, significant orbitopathy, and very large goiters or nodular thyroid disease are also suitable candidates.

Solitary Toxic Nodule and Toxic Multinodular Goiter

Toxic adenoma is a solitary nodule of the thyroid gland that produces excessive amounts of thyroid hormone and causes clinically overt hyperthyroidism. Malignancy in a toxic nodule is extremely rare. Unlike the diffuse goiter in Graves' disease, the thyroid gland is normal or small, with a palpable nodule that is "hot," or functional, on thyroid scan.

The initial treatment includes thionamides to normalize circulating thyroid hormone levels. Remission with medical management alone is rare. Thyroid lobectomy is the preferred management for solitary toxic nodule. After preoperative preparation with thionamine and possibly a beta blocker, the lobe with the "hot" nodule is excised by thyroid lobectomy and isthmusectomy.

Thyroidectomy is also the optimal therapy for a toxic multinodular goiter (Plummer's disease). Total thyroidectomy is indicated, especially if the goiter is large and associated with symptoms such as compression. In general, radioactive iodine ablation is not considered appropriate therapy for toxic adenoma or Plummer's disease. Although the overactive thyroid elements can be ablated, recurrence is common due to the intrinsic autonomy of the thyroid tissue.

Thyroid Carcinoma

In 2018, thyroid carcinoma was the 12th most common cancer in the United States with nearly 54,000 new cases. It is three times as common in women as in men, occurring primarily in those

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

25 to 65 years of age. The incidence of thyroid cancer, especially papillary carcinoma, has increased almost two-fold over the last decade. Thyroid cancers can arise from any of the cells that make up the gland including papillary or follicular carcinoma from follicular cells, medullary carcinoma from parafollicular cells. Hürthle cell or oncocytic carcinomas are a variant of follicular neoplasms that also arise from follicular cells. Poorly differentiated and anaplastic thyroid carcinomas likely arise from follicular cells but have lost cellular features present in well differentiated thyroid carcinomas.

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy in the United States, accounting for approximately 90% of cases. Characteristic cytologic features of PTC on FNA include cytoplasmic pseudoinclusions, nuclear grooves, and psammoma bodies. Tumors with a mixed papillary and follicular features are considered a follicular variant of papillary carcinoma and have similar biologic behavior to PTC.

Follicular thyroid carcinoma (FTC) is the second most common thyroid cancer, accounting for 5% to 10% of cases. It is more common in iodine-deficient areas of the world. Compared to papillary carcinoma, it is more common in older patients and has a more aggressive clinical course. On FNA, FTC has a monotonous, relatively uniform appearance of microfollicles, without the more complex papillations seen in papillary carcinoma. Cytology alone cannot distinguish between benign follicular adenoma and carcinoma. The definitive diagnosis requires histologic evaluation of the surgical specimen for capsular or vascular invasion. FNA specimens are often indeterminate, classified as follicular neoplasm or FLUS. Molecular testing may allow avoidance of diagnostic surgery in this patient population. Metastases from FTC are hematogenously disseminated to lung and bone. These lesions may be treated with RAI after the thyroid gland is removed. Lymph node metastases are uncommon.

Well differentiated thyroid carcinoma is treated with thyroidectomy. The extent of the disease including tumor size, extrathyroidal extension, lymph node involvement, patient's age, and comorbid conditions determines the extent of surgery: lobectomy or total thyroidectomy. Cervical lymph node status should be evaluated in all patients by preoperative ultrasound. Selected patients with locally advanced disease may undergo further imaging. Patients with evidence of lymph node metastasis from thyroid cancer, confirmed by FNA, undergo a therapeutic neck dissection of the involved central or lateral lymph node compartment at the time of thyroidectomy.

Following surgery, patients with high and intermediate risk for recurrence receive radioactive iodine treatment - typically at a dose four to five fold higher than RAI ablation for Graves' disease. Several risk stratifications systems are available to assess the risk of residual and recurrent disease. The American Thyroid Association (ATA) system is commonly used.

Well differentiated thyroid carcinoma responds to TSH. Postoperative thyroid hormone replacement therapy to maintain TSH at low normal range is indicated after total thyroidectomy and in many cases after thyroid lobectomy, to avoid a potential trophic effect on cancer cells.

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

High risk patients, or those with structural recurrence or incomplete response to therapy receive doses of levothyroxine to suppress the TSH below normal range.

After completion of treatment, patients are monitored for residual or recurrent disease using neck ultrasound and serum thyroglobulin if total thyroidectomy was performed. The frequency of monitoring and need for additional imaging is based on the initial risk stratification and response to treatment. The prognosis for papillary and follicular tumors is excellent with over 98% overall five-year survival and 99.9% five-year survival for those with localized disease confined to the thyroid at time of resection. Poor prognosis is associated with male sex, age older than 55 years, a primary tumor larger than 4 cm, less well differentiated subtypes, and locally invasive or distant metastatic disease.

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor of the C cells of the thyroid gland and constitutes less than 5% of all thyroid cancers. Calcitonin production is a characteristic feature. Most MTCs are sporadic in nature. Approximately 20% have a genetically transmitted, autosomal dominant inheritance pattern associated with multiple endocrine neoplasia syndrome type 2 (MEN2). Patients with advanced disease may present with diarrhea or facial flushing due to hormonal secretion by the tumor.

The diagnosis is usually suspected on FNA. Further evaluation includes measurement of serum calcitonin, carcinoembryonic antigen, and genetic testing for RET mutations and biochemical evaluation for coexisting tumors, especially pheochromocytoma. Treatment of MTC includes total thyroidectomy with central neck lymph node dissection. Lateral neck lymph node dissection is indicated if pathologic lymph nodes are identified on preoperative imaging or tumor markers calcitonin or CEA are markedly elevated. Patients with MTC have a worse prognosis than patients with well-differentiated papillary or follicular carcinoma; only 50% of patients survive 10 years.

Anaplastic carcinoma of the thyroid gland is an extremely aggressive neoplasm. It arises from the follicular cells, but is nearly completely dedifferentiated. Surgical resection does not appear to improve the outcome but can provide palliative relief of airway obstruction. The prognosis is dismal. Chemotherapy and external-beam radiation therapy are equally ineffective. Patients are all considered to have Stage IV disease at presentation, and few survive longer than 2 years.

PARATHYROID GLANDS

Anatomy

Normal parathyroid glands are tan, ovoid, fatty glands typically found on the posterior aspect of the thyroid gland. Each gland normally weighs 35mg and measures about 5mm in its greatest dimension. Most adults have four glands, however 10-15% can have additional normal sized glands or additional parathyroid “rests” from fragmentation of the glands during development. The embryologic development also determines the position of the parathyroid glands.

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

The superior parathyroid glands develop from the fourth branchial pouches, while the inferior parathyroid glands develop from the third branchial pouches and migrate caudally together with the thymus. Arterial supply is normally from inferior thyroid artery branches, and venous drainage is to the internal jugular, subclavian, and innominate veins. The superior glands generally lie posterior and lateral to the recurrent laryngeal nerve and superior to the inferior thyroid artery. The inferior glands are typically anterior and medial to the recurrent laryngeal nerve between the inferior thyroid pole and the superior aspect of the cervical thymus at the thyrothymic ligament. Any of the parathyroid glands can be ectopically positioned due to alterations in migration during embryologic development, though inferior glands are more often ectopic because of the longer path of migration. Ectopic locations are still along the path of migration often associated with other structures that develop with the 3rd and 4th branchial pouches. These locations include the carotid sheath, intrathyroidal, retrotracheal or retroesophageal, and the superior mediastinum.

Physiology

The parathyroid glands function to secrete parathyroid hormone (PTH) to maintain intravascular calcium homeostasis. Plasma PTH is rapidly cleaved into active N-terminal and inactive C-terminal fragments. The active fragment half-life is 3 minutes which results in rapid control of serum calcium levels. Hypocalcemia stimulates PTH secretion and hypercalcemia inhibits PTH secretion. PTH increases serum calcium via three distinct mechanisms: increases calcium resorption by the kidney; stimulates osteoclasts to release calcium from bone; and increases gastrointestinal absorption of calcium by stimulating hydroxylation of vitamin D to 1,25-dihydroxy-cholecalciferol in the kidney.

Primary Hyperparathyroidism

Primary hyperparathyroidism (PHP) occurs when one or more of the parathyroid glands becomes autonomous functioning, secreting PTH regardless of serum calcium levels. PHP is typically caused by a solitary benign adenoma in 85% of cases and multigland hyperplasia in 15% of cases. Parathyroid carcinoma is extremely rare. Most PHP is sporadic, but PHP is a common manifestation of MEN1.

Symptoms of PHP include neurocognitive dysfunction with fatigue being the most common complaint. Patients may experience memory or attention impairment or depressed mood. Due to routine screening laboratory testing for calcium and early stage of detection, PHP rarely causes severe psychiatric disturbance. Bone demineralization occurs from constitutive osteoclast activation which may lead to osteopenia, osteoporosis, or fragility fracture. Elevated serum calcium is filtered in the kidney and can cause hypercalciuria and subsequent nephrolithiasis. Gastrointestinal symptoms may also be present due to relaxation of enteric smooth muscle causing gastroesophageal reflux, bloating, or constipation. Severe hypercalcemia can cause pancreatitis. A family history of parathyroid disorder should also be obtained.

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

Evaluation begins by assessing serum calcium, PTH, vitamin D, and renal function. Though other diseases including malignancy may cause hypercalcemia, the differential diagnosis of hypercalcemia with elevated PTH includes: primary and tertiary hyperparathyroidism, familial hypercalcemic hypocalciuria (FHH), or lithium-induced hypercalcemia. FHH is a very rare autosomal dominant asymptomatic disease which causes lifelong hypercalcemia. Distinguishing primary hyperparathyroidism from FHH with a 24-hour urinary calcium measurement is necessary prior to surgical intervention, as patients with FHH will not benefit from surgery. Genetic analysis for FHH mutations in the calcium-sensing receptor should be performed to confirm the diagnosis if urinary calcium is low in the setting of hypercalcemia. The patient's medications should also be reviewed to exclude medication induced hypercalcemia, for example, from a thiazide diuretic.

Malignancy can also cause hypercalcemia, but will not cause an elevated PTH, except for a parathyroid carcinoma. Obtaining a serum parathyroid hormone-related peptide (PTHrP) level is indicated when occult malignancy is a concern and the PTH level is suppressed, indicating a paraneoplastic syndrome. The most common malignant causes of hypercalcemia are bronchial squamous cell carcinoma, bone destruction by primary cancers (e.g., multiple myeloma), or lytic bony metastases causing hypercalcemia without PTHrP elevation.

Parathyroidectomy is the mainstay of treatment for PHP.

NIH Criteria for Parathyroidectomy

- Age < 50 OR Any age with any of the following:
- Nephrolithiasis
- Osteitis fibrosa cystica
- Serum calcium >1.0 mg/dL above reference range (typically >11.2)
- Hypercalciuria (>400 mg/day)
- Bone mineral density T score reduced by >2.5 SD measured at one or more sites
- Creatinine clearance reduced by 30% compared to age-matched normal range
- History of an episode of life-threatening hypercalcemia
- Neuromuscular symptoms: proximal weakness, atrophy, hyperreflexia, and gait disturbance

Once a biochemical diagnosis of PHP is confirmed, imaging should be performed to attempt to localize a solitary adenoma and facilitate a focused exploration. Localization is performed with ultrasound, 4-dimensional computed tomography, and/or technetium-99 sestamibi nuclear medicine scan. If a single adenoma cannot be identified by imaging, a four gland exploration is performed. If a suspected adenoma is identified, a targeted operation with intraoperative PTH monitoring can be employed. For a successful focused operation the PTH level should fall by more than 50% from the preoperative baseline and in to the normal range within ten minutes of gland excision. Failure of the PTH level to drop appropriately necessitates continued neck exploration to evaluate the remaining glands. For hereditary causes of PHP such as MEN1, a four gland exploration is warranted.

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

The most serious complication of parathyroidectomy, recurrent laryngeal nerve injury, is rare. Persistent or recurrent hypercalcemia can occur in up to 5% of patients. Hypocalcemia can occur postoperatively due to suppression of remaining in situ glands or hungry bone syndrome where cessation of stimulation of osteoclasts leads to bone resorption of serum calcium. Calcium supplementation is necessary until the syndrome resolves.

Secondary and Tertiary Hyperparathyroidism

Secondary hyperparathyroidism (SHP) can occur because of low vitamin D levels or low calcium absorption related to nutritional deficiencies (e.g., malabsorptive disorders, bariatric surgery, obesity) or lack of sun exposure. SHP most commonly occurs as a consequence of renal failure. Impaired glomerular filtration causes phosphate retention and decreased serum calcium levels. Hydroxylation of vitamin D is also impaired leading to decreased gastrointestinal absorption of calcium and hypocalcemia. All parathyroid glands are stimulated to secrete PTH to restore calcium and phosphorous homeostasis. The multiple abnormalities in calcium, phosphate, and vitamin D metabolism have extremely deleterious effects on bone mineralization causing renal osteodystrophy and may also lead to calciphylaxis from soft tissue calcium deposition and resultant skin necrosis.

For end-stage renal disease patients, improved techniques of dialysis, vitamin D supplements, and effective oral phosphate binders have markedly enhanced the medical control of secondary hyperparathyroidism and decreased the incidence of significant bone disease. Cinacalcet, a calcimimetic that lowers calcium by activating the calcium-sensing receptor, is first line management for SHP. Subtotal parathyroidectomy is indicated for patients with refractory hyperparathyroidism or intolerance of calcimimetics. Total parathyroidectomy with autotransplantation of a portion of one gland is preferred by some surgeons to avoid the potential for reoperation in the neck if hyperparathyroidism recurs.

In tertiary hyperparathyroidism (THP), the hyperplastic glands in a patient with secondary hyperparathyroidism becomes an autonomous producer of PTH after the chronic stimulation of the glands from the secondary etiology has resolved, for example, after a kidney transplant for end stage renal disease. Once the secondary cause is treated, one or more parathyroid glands continues to overproduce PTH. Similar to PHP, patients with THP will have hypercalcemia. Operative management of THP includes 4-gland exploration with removal of any abnormal appearing glands guided by intraoperative PTH levels.

ADRENAL GLANDS

Anatomy

The adrenal glands are golden, triangular-shaped glands located behind the peritoneum of the posterior abdominal wall, closely associated with the upper poles of the kidneys. The right

ACS/ASE Medical Student Core Curriculum

Endocrine Diseases

adrenal gland lies posterior to the liver, and posterior and lateral to the inferior vena cava. The left adrenal is lateral to the aorta and just behind the superior border of the pancreatic tail.

The arterial blood supply to the adrenal glands is from three main arteries: the superior adrenal artery branches from the inferior phrenic artery, the middle adrenal artery arises from the aorta, and the inferior adrenal artery is a branch from the renal artery. The right adrenal vein drains directly into the inferior vena cava whereas the left adrenal vein drains into the left renal vein.

The adrenal gland is divided into two primary areas based on embryological development of the tissue types: the cortex, which is derived from mesoderm; and the medulla, which arises from neural crest cells. The medulla is the only endocrine organ gland whose activity is controlled entirely by nervous impulses. The innervation of the adrenal medulla is unusual in that there are no postganglionic cells.

Physiology

The adrenal cortex has three layers: the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis. Each zone produces its own distinct hormones derived from cholesterol. The cortical cells produce glucocorticoids, mineralocorticoids, and androgenic steroids.

The zona glomerulosa produces and secretes the mineralocorticoids aldosterone. Secretion of aldosterone is regulated by the renin–angiotensin system. In response to a decrease in renal blood flow, the juxtaglomerular cells within the kidney produce renin, which cleaves angiotensinogen into angiotensin I, which is then converted by angiotensin-converting enzyme (ACE) in the lung to angiotensin II. Angiotensin II directly stimulates aldosterone release from the zona glomerulosa, which increases the exchange of sodium for potassium and hydrogen ions in the distal nephron. Aldosterone stimulates renal sodium reabsorption while promoting potassium wasting to modulate the body's electrolyte composition, fluid volume, and blood pressure.

The cells within the zona fasciculata secrete the glucocorticoid cortisol, stimulated by circulating adrenocorticotropic hormone (ACTH) from the anterior pituitary and suppressed by cortisol feedback inhibition. Cortisol is involved in the intermediate metabolism of carbohydrates, proteins, and lipids. It increases blood glucose levels by decreasing insulin uptake and stimulating hepatic gluconeogenesis. Cortisol also slows amino acid uptake and peripheral protein synthesis while increasing peripheral lipolysis. Prolonged effects of high levels of cortisol include induction of a catabolic state, proximal muscle wasting, truncal obesity, insulin-resistant diabetes, impaired wound healing, and immunosuppression.

The cells of the zona reticularis respond to ACTH by converting pregnenolone to 17-hydroxypregnenolone, which is then converted to dehydroepiandrosterone (DHEA), the major sex steroid produced by the adrenal glands. DHEA is converted by local tissues into

testosterone. Adrenal production of sex hormones is responsible, in part, for the development of male secondary sexual features. Abnormal production can cause virilization in women.

Cushing's Syndrome and Cushing's Disease

Cushing's syndrome (CS), refers to the signs and symptoms of hypercortisolism, whereas Cushing's disease (CD) is hypercortisolism due to an ACTH-producing pituitary adenoma. CS may be ACTH dependent or independent. ACTH-independent CS may be caused by exogenous steroid administration, cortisol producing adrenal adenomas, adrenocortical carcinoma (ACC), or bilateral adrenal hyperplasia. ACTH-dependent CS may be from CD with a pituitary adenoma producing excess ACTH, or extrapituitary tumors such as small cell lung cancer or bronchial carcinoid producing ACTH.

CS is four times more common in women than men. Signs and symptoms include truncal obesity, hypertension, hyperglycemia, weakness, striae, hirsutism, moon facies, and lipodystrophy of the dorsocervical fat pad. There are three main screening tests in the evaluation of CS: 24 hour urinary free cortisol, late-night salivary cortisol, and low dose 1-mg overnight dexamethasone suppression test (DST). An abnormal finding on one of these tests should prompt an additional confirmatory test. If CS is confirmed and ACTH is suppressed, the etiology is from an adrenal tumor. The patient should be evaluated with CT scan to localize the adrenal mass. If the ACTH level is normal or increased, then the patient should have a pituitary MRI to evaluate for a pituitary tumor.

Solitary, unilateral, benign adenomas are the cause of primary adrenal hypercortisolism in 90% of patients. The treatment of choice is laparoscopic unilateral adrenalectomy. All of these patients should receive perioperative stress steroids with taper.

Primary Hyperaldosteronism

Primary hyperaldosteronism (PA), (Conn's syndrome), is defined as inappropriate hypersecretion of aldosterone in the absence of activation of the renin-angiotensin system. The syndrome is twice as common in women as in men, and most commonly occurs between the fourth and the sixth decades of life. PA has been reported in more than 10% of hypertensive patients, 20% of patients with resistant hypertension. Although the classic presentation of PA is hypertension and hypokalemia, only 30% of patients will have hypokalemia on presentation. The importance of diagnosing PA is that it may be surgically curable, and these patients have higher cardiovascular morbidity and mortality than matched patients with hypertension of other etiologies.

The diagnosis is suspected in patients with moderate or severe hypertension or drug-resistant hypertension, hypertension and hypokalemia, hypertension and an adrenal lesion, or hypertension in a patient with a family history of PA, early-onset hypertension, or the sequelae of hypertension. Sixty percent of these patients have an adrenal adenoma, while 40% have bilateral hyperplasia.

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

An aldosterone-to-renin ratio (ARR) is the best initial screening test. An ARR greater than 30 is definitive for a diagnosis of PA. Once PA has been confirmed, all patients should have a CT scan of the abdomen. Adrenal vein sampling for aldosterone levels in the bilateral adrenal veins is used to confirm that a lesion found on cross-sectional imaging is the source of hypersecretion.

Patients with unilateral aldosteronomas should have their hypertension and hypokalemia normalized prior to surgical intervention, often with a mineralocorticoid receptor antagonist such as spironolactone. Laparoscopic unilateral adrenalectomy is the treatment of choice in these patients. When adenomas are removed, the blood pressure becomes normal in 70% of cases; the remainder will require modest antihypertensive therapy. Patients with hyperaldosteronism that cannot be localized to one adrenal gland are managed with spironolactone and symptomatic treatment. In most of these patients, bilateral adrenal hyperplasia (diffuse disease) is the cause of the hyperaldosteronism, and bilateral adrenalectomy is not recommended.

Pheochromocytoma

Pheochromocytomas are tumors arising from catecholamine-producing chromaffin cells in the adrenal medulla. Most are hormonally active producing norepinephrine (NE) and epinephrine (EPI). Extra-adrenal lesions are classified as paragangliomas. These extra-adrenal sites may be anywhere from the base of the skull to the pelvis, but most are para-aortic. Ninety-eight percent of pheochromocytomas are located in the abdominal cavity. In order to convert NE to EPI, phenylethanolamine-N-methyltransferase (PNMT) must be induced. Extra-adrenal paragangliomas do not have this activated enzyme and thus usually only secrete NE. Plasma normetanephrine levels are elevated in 97% of patients with adrenal pheochromocytoma and 100% of patients with paraganglioma.

Most patients present with episodic hypertension associated with palpitations, headache, and sweating. Patients may also experience a sense of impending doom, significant anxiety, weight loss, and constipation. Physical signs of an attack may include pallor, flushing, and sweating. Most attacks are short-lived, but can be precipitated by trauma including medical procedures, physical activity, exertion, changes in position, alcohol intake, micturition, smoking, or labor. Pheochromocytoma typically presents as a sporadic tumor, but may also be found as a part of the MEN syndromes 2A and 2B. Pheochromocytomas are also associated with many familial disorders, including von Recklinghausen's disease, von Hippel-Lindau syndrome, Sturge-Weber syndrome, and succinate dehydrogenase deficiencies.

Evaluating patients for pheochromocytoma or functional paraganglionoma includes plasma-free metanephrine and normetanephrine with confirmatory 24-hour urine catecholamines and metanephrines, chest and abdominal CT or MRI. All patients diagnosed with a pheochromocytoma should undergo genetic counseling. If there is a suspicion of multiple tumors, or if CT is negative, DOTATATE Gallium-68 PET scan is indicated which is more accurate than MIBG (metaiodobenzylguanidine) scan.

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

Once the diagnosis of pheochromocytoma is confirmed, patients should be started on alpha-blockade (phenoxybenzamine or doxazosin). Doses should be increased until adequate alpha blockade is achieved. After the patient is alpha blocked, beta-blockade is used prior to surgery or if the patient is tachycardic. It is critical to initiate beta-blocker therapy only after adequate alpha blockade has been achieved.

If the pheochromocytoma is resectable, laparoscopic adrenalectomy is the procedure of choice. Patients must have long-term follow-up after resection because 10% to 15% of patients with pheochromocytoma will recur.

Adrenal Cortical Carcinoma

ACCs are rare tumors with a worldwide incidence of 2 per million people annually. Although they can occur at any age, they demonstrate a peak they are most commonly diagnosed in the fourth and fifth decades. They are usually unilateral, and symptoms are most often related to hormone hypersecretion found in up to 60%. The prognosis is generally poor with up to 70% of patients presenting with metastatic disease. Poor prognosis is related to advanced stage at detection and incomplete surgical resection.

CT scan is the imaging modality of choice for adrenal lesions. Features on abdominal CT that suggest that an adrenal mass is a carcinoma include size greater than 6cm, irregular borders, heterogeneity, evidence of central necrosis, stippled calcifications, regional adenopathy, invasion of adjacent structures, and the presence of metastases.

The treatment of choice is surgical excision with total gross tumor removal. Even in the setting of metastatic disease, resection is indicated for functional masses. The overall prognosis of ACC is poor with a five year survival of 30%. Survival has been relatively unchanged for the past 30 years.

Adrenal Incidentaloma

With increasing use of CT, MRI, and ultrasound, incidentally discovered adrenal masses have become the most common presentation, so called adrenal "incidentalomas." These lesions are typically asymptomatic, and therefore present a unique challenge for the managing physician. The prevalence of an adrenal incidentaloma has been estimated at 5% when upper abdominal CT scans are evaluated.

For all incidentalomas greater than 1cm in size, it is essential to assess for functionality with clinical and laboratory evaluation regardless of symptoms. The diagnostic approach to the adrenal incidentaloma should consist of clinical, laboratory, and imaging evaluation to assess for hypercortisolism, aldosteronism, pheochromocytoma, or a malignant adrenal lesion. Approximately 80% of incidentally discovered adrenal masses are nonfunctioning adenomas, 5% are subclinical cortisol secreting CS, 5% are pheochromocytoma, 1% are aldosteronoma, <5% are adrenocortical carcinomas, and 2.5% are metastases to the adrenal gland.

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

To assess for Cushing's Syndrome, the 1-mg overnight DST is a good initial screening test. Pheochromocytoma should be assessed with serum metanephrines. Hyperaldosteronism should be assessed with serum aldosterone to renin ratio.

The next step is to determine if the lesion has radiographic findings concerning for malignancy. A lesion less than 4cm with regular borders and low density that is not producing hormones based on biochemical testing can be monitored with repeat CT scan. If imaging shows a mass >4cm or suspicious features such as high density or irregular borders, or the lesion is functional creating hormone excess, an adrenalectomy should be performed. Biopsy of an adrenal lesion should only be performed to evaluate for metastatic disease in a patient with a known cancer history, after biochemical evaluation excludes pheochromocytoma.

Multiple Endocrine Neoplasia Syndromes

The hereditary syndromes of the endocrine and neuroendocrine glands are collectively referred to as Multiple Endocrine Neoplasia (MEN) syndromes and encompass MEN type 1, MEN type 2 - including 2A and 2B. These syndromes are a group of heritable tumors which may be benign or malignant. MEN1, also known as Wermer Syndrome, is associated with primary hyperparathyroidism, duodenopancreatic neuroendocrine tumors (NET), and pituitary tumors and is caused by a germline mutation in the MEN1 gene. The MEN2 syndromes include medullary thyroid cancer (MTC), pheochromocytoma (PHEO), and parathyroid adenomas or hyperplasia. MEN2 is caused by germline mutations in the RET gene. MEN2 is further divided into type 2A, type 2B, or familial medullary thyroid carcinoma (FMTC).

Multiple Endocrine Neoplasia Type 1

MEN1 is a mutation in the MEN1 gene inherited in an autosomal dominant fashion. The MEN1 gene encodes the protein menin. The manifestations of MEN1 have variable penetrance and include: primary hyperparathyroidism (PHP), duodenopancreatic NET, and pituitary tumors. Clinical features are used to diagnose MEN1 with two of the three manifestations. Familial MEN1 is defined as at least one of the features with one first degree relative that has one or more of these tumors, or two first degree relatives with a known germline mutation. Patients typically present with initial symptoms between 20 and 30 years of age.

The most common manifestation and frequently the first presenting sign of MEN1 is PHP. Unlike sporadic PHP, MEN1 patients have multigland parathyroid hyperplasia and present in the third decade of life. Surgery for PHP in MEN1 patients should include exploration of all parathyroid glands, subtotal (3-3.5 gland removal) parathyroidectomy or total parathyroidectomy with reimplantation of parathyroid in the sternocleidomastoid or brachialis muscle. While total parathyroidectomy with reimplantation has lower recurrence rates, it has the added risk of permanent hypoparathyroidism. Additionally, cervical thymectomy should be performed during the index operation to mitigate the risk of recurrent PHP and thymic carcinoid in the future. Recurrence rates for PHP in MEN1 are high and patients may require remedial parathyroidectomy.

ACS/ASE Medical Student Core Curriculum
Endocrine Diseases

Duodenopancreatic neuroendocrine tumors are the second most common endocrine manifestation in MEN1, occurring in up to 80% of patients by age 40 years. These tumors may be nonfunctional or hypersecreting with gastrinoma, insulinoma, vasoactive intestinal peptide tumor (VIPoma), glucagonoma, or somatostatinoma.

Multiple Endocrine Neoplasia Type 1 Duodenopancreatic Neuroendocrine Tumors - Penetrance and Clinical Features

Tumor type	Estimated Penetrance	Symptoms
Gastrinoma	≤70%	Peptic ulcer disease
		Diarrhea
		Abdominal pain
		Weight loss
Nonfunctioning	20%–55%	Symptoms from local compression or obstruction
Insulinoma	10%	Whipple’s triad: fasting symptomatic hypoglycemia, relieved by glucose
Vasoactive intestinal peptide	1%	Watery diarrhea
		Hypokalemia
		Achlorhydria
Glucagonoma	1%	Diabetes mellitus
		Diarrhea
		Depression
		Necrolytic migratory erythema
		Thromboembolic disease
Somatostatinoma	<1%	Diabetes mellitus
		Diarrhea
		Cholestasis
		Hypochlorhydria
		Weight loss

Up to half of MEN1 patients will develop a pituitary tumor. Two-thirds of these are microadenomas (<1.0 cm in diameter), and the majority of these tumors are prolactin-secreting with an estimated penetrance of 20%. Prolactinomas may cause symptoms of galactorrhea, amenorrhea, dysmenorrhea, or hypogonadism. Other pituitary tumors can include somatotropinomas and corticotropinomas, or they may be nonfunctioning. Medical therapy to suppress hypersecretion is the first line of therapy for MEN1-associated pituitary tumors. Surgery is often necessary for patients who are resistant to this treatment or who develop macroadenomas or symptoms of compression. Radiation therapy may be used for patients with incomplete surgical resection.

Multiple Endocrine Neoplasia Syndrome Type 2

The MEN2 syndrome pathology includes medullary thyroid cancer (MTC), pheochromocytoma (PHEO), and primary hyperparathyroidism with parathyroid adenoma or hyperplasia. MEN2 is inherited in an autosomal dominant fashion with a defect in the RET (REarranged during

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

Transfection) proto-oncogene which encodes a tyrosine kinase receptor. The majority of cases are subtype 2A.

The MEN2 syndrome has subclassifications based on the additional clinical characteristics in the patient or their family cohort. MEN2A, or Sipple syndrome, includes MTC, PHEO and/or PHP with additional features of cutaneous lichen amyloidosis, or Hirschsprung disease. Features of MEN2B are mucosal neuromas of the lips and tongue, thickening of corneal nerve fibers, distinctive facies with enlarged lips, a Marfanoid body habitus, and MTC. An additional subtype of MEN2 is familial medullary thyroid carcinoma (FMTC) which includes a RET mutation and MTC but no family or personal history of PHEO or PHP.

Patients with MEN2 associated MTC present at an earlier age than the sporadic cases, which typically occur in the fifth or sixth decade of life. MEN2 should be suspected when MTC occurs at an early age, or is multifocal or bilateral. Up to 95% of patients with MEN2A will develop MTC. Survival is correlated with stage at diagnosis, and decreased survival in MTC can be accounted for in part by a high proportion of late-stage diagnosis. Survival rates for MTC with disease confined to the thyroid gland approaches 96% at 10 years, and are the rationale for risk-reducing thyroidectomy in MEN2. MEN2 patients undergoing thyroidectomy for MTC should be screened for PHEO with plasma metanephrine and normetanephrine assays.

Risk-reducing thyroidectomy is the preferred treatment strategy for patients with MEN2. Timing of surgery depends on the risk classification based on specific RET codon mutation as well as periodic thyroid ultrasound and calcitonin assay. Children with moderate risk mutations should have physical examination, ultrasound of the neck, and measurement of the serum calcitonin beginning around age 5 years. Children with negative calcitonin may be followed at semi-annual or annual intervals. Timing of surgery should be determined by a multidisciplinary group of pediatrician, endocrinologist, and surgeon in conjunction with the child's parents based on the findings of screening evaluations. Total thyroidectomy with or without central neck lymph node dissection is indicated in these patients.

PHEO can be sporadic or associated with MEN2 which should be suspected in cases of bilateral or multifocal PHEO, age less than 35 years, or personal or family history of MTC or PHP. MEN2-associated PHEOs are less likely to be malignant than those from sporadic disease. For known MEN2 patients, screening for PHEO should be considered by age 11 for high-risk mutations and age 16 for moderate risk with periodic plasma metanephrines. Imaging should be obtained to localize tumors in those who have elevated results.

PHP in MEN2 has less severe manifestations than in MEN1, often with only mild hypercalcemia. The pathology is more likely from solitary adenoma rather than multigland hyperplasia than in MEN1, but still have higher rates of multigland disease (50%) than the sporadic population (85%). PHP is rarely the initial manifestation of MEN2. Most patients with MEN2 related PHP are incidentally diagnosed at the time of thyroidectomy for MTC. Otherwise, surgical indications for MEN2 associated PHP are similar to those for sporadic disease. Due to the high rates of multigland hyperplasia, a four-gland exploration is recommended. Recurrence rates for PHP

ACS/ASE Medical Student Core Curriculum Endocrine Diseases

after parathyroidectomy are lower for MEN2 than for MEN1, but still higher than the sporadic population.

The MEN2B subtype, mucosal neuroma or Wagenmann-Frobese syndrome, accounts for about 5% of MEN2 cases and is characterized by oral mucosal neuromas, a Marfanoid body habitus, and early onset aggressive MTC with complete penetrance. PHEOs occur in about 50% of MEN2B cases; about half are multiple and often bilateral. Symptomatic PHP is very uncommon in this cohort. Nearly half of MEN2B patients will also have diffuse ganglioneuromatosis of the gastrointestinal tract.

Genetic testing can classify individuals at highest risk of MTC based on the RET variant detected. Those with MEN2B and RET codon M918T are associated with the youngest age of MTC and highest disease mortality which can inform timing of thyroidectomy. Total thyroidectomy should be considered by one year of age in the highest risk patients with M918T mutations. Children with other high-risk mutations may undergo prophylactic thyroidectomy at age 5 years or earlier, on the basis of the serum calcitonin levels.

References

1. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1.
2. Wells SA Jr, Asa SL, Dralle H, et al.: Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 25 (6): 567-610, 2015.
3. Bilezikian J.P., Brandi M.L., Eastell R., et al: Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; 99:3561-3569.
4. Wilhelm S.M., Wang T.S., Ruan D.T., et al: The American association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA surgery* 2016; 151:959-968.
5. Lee JM, Kim MK, Ko SH, et al. Clinical Guidelines for the Management of Adrenal Incidentaloma. *Endocrinol Metab.* 2017;32(2):200-218.
6. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab* 97 (9): 2990-3011, 2012.

Authors/Contributors

Marc deMoya, MD, FACS (Section Editor)
Medical College of Wisconsin, Milwaukee, WI

Abbey L. Fingeret, MD, FACS (Goals and Objectives, Content Author)
University of Nebraska, Omaha, NE