Pathology of the endocrine system

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THE ENDOCRINE SYSTEM

- Group of glands that maintain body homeostasis.
- Functions by release of hormones that travel via blood to distant organs.
- "Feedback" mechanisms control hormone release.
- Anatomically, the endocrine system consists of:
  - **Six distinct organs**: pituitary, adrenals, thyroid, parathyroids, gonads, and pancreatic islets.
  - **Neuroendocrine system** which is consist of cells dispersed singly or in small group throughout various non-endocrine organ including G.I.T. lung. Skin.
In general, pathologic processes affecting endocrine glands with resultant hormonal abnormalities may occur from following processes

- **Hyperfunction:** Excess of hormone secreting tissues.

- **Hypofunction:** Deficiency of hormones.

- **Hormone resistance:** There may be adequate or excessive production of a hormone but there is peripheral resistance.
THYROID GLAND

- Normal adult gland (weighing 15-30 g) consists of two lateral lobes connected by isthmus.

- Microscopically: It consists of thyroid follicles lined by cuboidal epithelium & containing colloid. The lobules are enclosed by fibrovascular septa. Calcitonin-secreting C-cells or parafollicular cells are dispersed within the follicles.

- Responsible for the secretion of:
  - Thyroid hormones (T3 and T4) required for the development of brain and maintenance of basal metabolic rate.
  - Calcitonin is involved in calcium homeostasis.

- The two types of disorders associated with this gland are hyperthyroidism and hypothyroidism.
Thyroid hormones (T3 and T4)

Increased metabolism
Growth and development
Increased catecholamine effect

Negative feedback

Thyrotropin-releasing hormone (TRH)
Thyroid-stimulating hormone (TSH)

Anterior pituitary gland
Hypothalamus
**HYPERTHYROIDISM**

*Thyrotoxicosis* is a hypermetabolic state caused by elevated circulating levels of free T3 and T4. Because it is caused most commonly by hyperfunction of the thyroid gland, it is often referred to as *hyperthyroidism*.

However, in certain conditions the oversupply is related to either excessive release of preformed thyroid hormone (e.g., in thyroiditis) or to an extrathyroidal source, rather than hyperfunction of the gland. Thus, strictly speaking, hyperthyroidism is only one cause of thyrotoxicosis.

- **primary hyperthyroidism** arising from an intrinsic thyroid abnormality
- **Secondary hyperthyroidism** arising from processes outside of the thyroid, such as a TSH-secreting pituitary tumor.
Causes of thyrotoxicosis

<table>
<thead>
<tr>
<th>Associated with Hyperthyroidism</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
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<tr>
<td>Diffuse hyperplasia (Graves disease)</td>
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<tr>
<td>Hyperfunctioning (“toxic”) multinodular goiter</td>
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<tr>
<td>Hyperfunctioning (“toxic”) adenoma</td>
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<tr>
<td><strong>Secondary</strong></td>
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<tr>
<td>TSH-secreting pituitary adenoma (rare)*</td>
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<table>
<thead>
<tr>
<th>Not Associated with Hyperthyroidism</th>
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<tbody>
<tr>
<td>Granulomatous (de Quervain) thyroiditis <em>(painful)</em></td>
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<tr>
<td>Subacute lymphocytic thyroiditis <em>(painless)</em></td>
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<tr>
<td>Struma ovarii (ovarian teratoma with ectopic thyroid)</td>
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<tr>
<td>Factitious thyrotoxicosis (exogenous thyroxine intake)</td>
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Clinical features of hyperthyroidism

Symptoms of hyperthyroidism are caused by hypermetabolism and excessive stimulation of the sympathetic system. Increased metabolic rate is accompanied by hyperactivity and subsequent fatigue, heat intolerance, and weight loss. The most important signs and symptoms related to major organ systems are:

- **Cardiovascular system**: Tachycardia, increased cardiac output, increased incidence of atrial fibrillation, and palpitations
- **Nervous system**: Nervousness, anxiety, hyperkinesia, and tremor
- **Skeletal muscles**: Muscle weakness and wasting
- **Gastrointestinal system**: Increased appetite, intestinal hypermotility, and diarrhea
- **Skin**: Excessive sweating
- **Bones**: Osteoporosis
Graves’ Disease  (DIFFUSE TOXIC GOITRE)

It is the *commonest cause* of hyperthyroidism characterized by the **triad** of:

- **Hyperthyroidism** due to hyperfunctional diffuse enlargement of gland.
- **Infiltrative ophthalmopathy** due to increased volume of retro-orbital connective tissue *by orbital fibroblasts*.
- **Localized, infiltrative dermopathy** (also called as *pretibial myxedema*).

The disorder is more common in **females** of the age group of 20-40 years.
**Pathogenesis:**

It is an autoimmune disease most commonly due to formation of antibodies to:

1. **TSI** (called *Thyroid Stimulating Immunoglobulin*) in which the antibodies stimulate the TSH receptor.
2. **TGI** (Thyroid Growth stimulating Immunoglobulin)
3. **TBII** (TSH Binding Inhibitor Immunoglobulin), the latter sometimes responsible for *paradoxical hypothyroidism* seen in some of these patients.

**Morphology:**

- **Grossly** the thyroid gland is symmetrically enlarged. Increases in weight to over 80gm are not uncommon.

On cut section, the parenchyma has a soft, meaty appearance resembling muscle.

- **Histologically,** the follicular epithelial cells are hyperplastic, tall and more crowded than usual with small papillae, which project into the follicular lumen, sometimes filling the follicles.

The colloid within the follicular lumen is pale, with scalloped margins.

Lymphoid infiltrates, consisting predominantly of T cells, along with scattered B cells and mature plasma cells, are present throughout the interstitium. Germinal centers are common.
Investigations reveal:

- Increased levels of T3 and T4
- Reduced TSH levels.
Accumulation of loose connective tissue behind the orbits also adds to the protuberant appearance of the eyes.
Graves disease

Diffuse symmetric enlargement of the gland and a beefy deep red parenchyma

The follicles are lined by tall, columnar epithelium. The crowded, enlarged epithelial cells project into the lumens of the follicles. These cells actively resorb the colloid in the centers of the follicles, resulting in the scalloped appearance of the edges of the colloid.
HYPOTHYROIDISM

It is caused due to decreased secretion of the thyroid hormones either due to:

- **Primary** defect in the thyroid *(most common)*
  - Developmental.
  - Surgery, external radiation.
  - Auto-immune (i.e., Hashimoto’s).
  - Iodine deficiency.

- **Secondary** (TSH deficiency, pituitary)

- **Tertiary** (TRH deficiency, hypothalamic) cause.
Clinical features of hypothyroidism

The clinical manifestations of hypothyroidism, depending upon the **age at onset of disorder**, are divided into 2 forms:

1. **Cretinism or congenital hypothyroidism** is the development of severe hypothyroidism during infancy and childhood.
2. **Myxoedema** is the adulthood hypothyroidism.

The clinical features of the disease, are the opposite of those of thyrotoxicosis, include lethargy, sensitivity to cold, reduced cardiac output, constipation, *myxedema* [due to accumulation of glycoaminoglycans, proteoglycans and water resulting in deep voice, and non- pitting edema of hands and feet] and menorrhagia (increased menstrual blood loss).
Cretinism

- Severe retardation
- Short stature
- Protruding tongue
- Umbilical hernia
Myxedema

- Lethargy
- Sensitivity to cold
- Reduced cardiac output
- Constipation
- ↑Cholesterol
The diagnosis is made using serum TSH. It is the most useful screening test.

- Serum TSH is elevated in primary hypothyroidism
- Serum TSH is reduced in secondary and tertiary hypothyroidism.
The adrenal glands are paired endocrine organs consisting of both cortex and medulla, which differ in their development, structure, and function. The cortex being mesodermal and the medulla of neural origin.
Adrenal cortex

The adrenal cortex synthesizes three different types of steroids:

1. Mineralo corticoids, the most important being aldosterone which is generated in the zona glomerulosa.
2. Glucocorticoids "principally cortisone" which are synthesized primarily in the Zona fasciculata.
3. Sex steroid "eostrogens and androgens", which are produced largely in the zona reticularis.
Hyperadrenalism

It has 3 distinctive patterns:

1. **Hyperaldosteronism**: Excess of mineralocorticoids
2. **Cushing syndrome**: Excess of glucocorticoids
3. **Adrenogenital syndrome**: Excess of sex steroids (androgens)
CUSHING SYNDROME (Hypercortisolism)

**Definition**: disorder caused by conditions that produce elevated glucocorticoid levels.

**Pathogenesis**: Cushing syndrome can be broadly divided into exogenous and endogenous causes.

1. The vast majority are the result of the administration of exogenous glucocorticoids (“iatrogenic” Cushing syndrome).

2. The endogenous causes can, in turn, be divided into those that are ACTH dependent and those that are ACTH independent

   A. **ACTH dependent**:
      - Hypothalamic-pituitary diseases associated with hyper secretion of ACTH "Cushing disease", ACTH-secreting pituitary adenomas account for 70%.
      - Secretion of ectopic ACTH by nonendocrine neoplasma e.i.g. " oat cell carcinoma of lung, medullary thyroid carcinoma carcinoid tumour, islet cell tumour of the pancreas.

   B. **ACTH independent**: Primary adrenocortical hyperplasia or neoplasia “ 10-20%".
HPA Axis

Hypothalamus

CRH

Corticotropin Releasing Hormone

Anterior Pituitary

ACTH

Adrenocorticotropic Hormone

Adrenal Cortex

CORT

Cortisol

Negative Feedback
Schematic representation of the various forms of Cushing syndrome: The three endogenous forms, as well as the more common exogenous (iatrogenic) form. ACTH, adrenocorticotropic hormone.
Clinical features

The symptoms and signs of Cushing can be remembered with the mnemonic buffalo hump:

- Buffalo hump
- Unusual behavior (depression, personality changes, and fatigability)
- Facial features (moon face, hirsutism in women)
- Fat accumulation (obesity)
- ACTH (and cortisol) in blood; ACTH and dexamethasone test abnormalities
- Loss of muscle mass (thin legs and arms; protruding abdomen due to weak abdominal muscles)
- Overextended skin (striae with easy bruise ability due to weak vessels)
- Hypertension
- Urinary cortisol and 17-hydroxycorticosteroids
- Menstrual irregularities
- Osteoporosis
**Morphology:**

The morphologic features in the adrenal vary from:

- Bilateral cortical atrophy in *exogenous* steroid-induced disease.
- Bilateral diffuse or nodular hyperplasia, to an adrenocortical neoplasm in *endogenous* Cushing syndrome.

**Diagnosis:**

There is an increased 24 hour free cortisol level in the urine with loss of normal diurnal pattern of cortisol secretion. For differentiating between the causes of Cushing syndrome, we use *dexamethasone suppression test.*
A patient with Cushing syndrome demonstrating central obesity, “moon facies,” and abdominal striae.
Diffuse hyperplasia of the adrenal contrasted with normal adrenal gland. In cross-section the adrenal cortex is yellow and thickened, and a subtle nodularity is seen.
Adrenogenital Syndromes

Excess of androgens may be caused by a number of diseases including:

- primary gonadal disorders.
- primary adrenal disorders.

The adrenal causes of androgen excess include an uncommon group of disorders collectively designated congenital adrenal hyperplasia (CAH).
Congenital adrenal hyperplasia

- Group of **autosomal recessive** disorders, each characterized by a hereditary defect in an enzyme involved in adrenal steroid biosynthesis, particularly **cortisol**.

- In these conditions, decreased cortisol production results in a compensatory **increase in ACTH secretion** due to absence of feedback inhibition, which in turn **stimulates androgen production**.

- Androgens have virilizing effects, including masculinization in females (ambiguous genitalia, oligomenorrhea, hirsutism), precocious puberty in males with oligospermia in older patients, and in some instances, salt (sodium) wasting and hypotension.

- The most common enzymatic defect in CAH is **21-hydroxylase deficiency**, which accounts for more than 90% of cases.
Morphology

- **Bilateral hyperplasia of the adrenal cortex** is characteristic, sometimes expanding to 10 to 15 times their normal weights.

- In addition to cortical abnormalities, **adrenomedullary dysplasia** also has recently been reported in patients with the salt-losing 21-hydroxylase deficiency.
ADRENAL INSUFFICIENCY (Hypoadrenalism)

Adrenocortical insufficiency, or hypofunction, may be caused by:
- Primary hypoadrenalism due to primary adrenal disease.
- Secondary hypoadrenalism due to Hypothalamic Pituitary Disease that leads to ACTH deficiency.

The patterns of adrenocortical insufficiency can be divided into:

(1) Primary adrenocortical insufficiency.
   - Acute adrenocortical insufficiency (adrenal crisis)
   - Chronic adrenocortical insufficiency (Addison disease)

(2) Secondary adrenocortical insufficiency.
Primary acute adrenocortical insufficiency

Causes
- Stress
- Sudden withdrawal of steroids
- Massive adrenal hemorrhage.

Acute adrenal insufficiency is associated with *bilateral hemorrhagic infarction* of the adrenal glands associated with a *Neisseria infection* (septicemia) in a child, it can result in disseminated intravascular coagulation and rapidly developing hypotension and shock in the patient which is called **Waterhouse-Friedrichsen Syndrome**. The hemorrhage in this condition usually begins in the medulla and then involves the cortex.
These adrenals are black-red from extensive hemorrhage in a patient with septicemia.
Adrenal gland massively replaced by hemorrhage. There was no evidence of a tumor in any of the many sections taken.
Waterhouse-Friderichsen syndrome. At autopsy, the adrenals were hemorrhagic with little residual cortical architecture is discernible.
Primary chronic adrenocortical insufficiency (Addison disease)

It is an uncommon disorder resulting from progressive destruction of the adrenal cortex.

Causes
1. Autoimmune adrenalitis: (60–70% of cases in developed countries)
2. Infection: Tuberculosis, Acquired immunodeficiency syndrome, Fungal infections
3. Metastatic neoplasms.
4. Systemic amyloidosis.
5. Hemochromatosis.

Clinical features
progressive weakness and easy fatigability, gastrointestinal disturbances like anorexia, nausea, vomiting, weight loss and diarrhea.

In patients with primary adrenal disease, increased circulating levels of ACTH precursor hormone stimulate melanocytes, with resultant hyperpigmentation of the skin particularly of sun-exposed areas and at pressure points, such as neck, elbows, knees, and knuckles.
Hyperpigmentation of hands and palmar creases
Morphology

The anatomic changes in the adrenal glands depend on the underlying disease.

Primary autoimmune adrenalitis is characterized by irregularly shrunken glands, which may be difficult to identify within the suprarenal adipose tissue. Histologically the cortex contains only scattered residual cortical cells in a collapsed network of connective tissue. A variable lymphoid infiltrate is present in the cortex and may extend into the adjacent medulla, although the medulla is otherwise preserved.

Tuberculous and fungal disease, the adrenal shows a granulomatous inflammatory reaction. Metastatic carcinoma, the adrenals are enlarged and the normal architecture is obscured by the infiltrating neoplasm.
Autoimmune adrenalitis. In addition to loss of all but a subcapsular rim of cortical cells, there is an extensive mononuclear cell infiltrate.
Enlargement of the gland by a markedly hemorrhagic tumor representing metastatic breast carcinoma.
Secondary adrenocortical insufficiency

It occurs secondary to any disorder of the hypothalamus and pituitary, such as metastatic cancer, infection, infarction, or irradiation.
ADRENAL MEDULLA

• The adrenal medulla is composed of **neuroendocrine cells** called chromaffin cells and their supporting cells called sustentacular cells.

• The organ is responsible for the secretion of **epinephrine** and **nor-epinephrine** and is controlled by the autonomic nervous system.
PHEOCHROMOCYTOMA

It is a tumor of the adrenal medulla which produces catecholamines. The patients usually have severe headache, anxiety, increased sweating, tachycardia, palpitations and hypertensive episodes.

The tumor is associated with a ‘rule of 10’s’ consisting of:
- 10% are bilateral
- 10% are extra-adrenal
- 10% are malignant
- 10% occur in children
- 10% are not associated with hypertension

Morphology

Presence of small or large tumors that have yellow tan color that turns brown on incubation. There is presence of nests of chief or chromaffin cells with sustentacular cells (called zellballen) with abundant cytoplasm which contains catecholamine granules. The nuclei of the cells have ‘salt and pepper’ appearance of the chromatin. The immunomarkers for this tumor include chromogranin and synaptophysin in chief cells and S-100 for sustentacular cells.

The definitive diagnosis of malignancy is based exclusively on the presence of metastasis.

Investigations

Presence of elevated urinary excretion of free catecholamines and their metabolites such as vanillylmandelic acid (VMA) and metanephrines.
Pheochromocytoma. The tumor is enclosed within an attenuated cortex and demonstrates areas of hemorrhage. The comma shaped residual adrenal is seen below.
Pheochromocytoma, demonstrating characteristic nests of cells (Zellballen) with abundant cytoplasm. Granules containing catecholamine are not visible in this preparation. It is not uncommon to find bizarre cells even in pheochromocytomas that are biologically benign, and this criterion by itself should not be used to diagnose malignancy.
THANK YOU