BIOS222
Pathology and Clinical Science 2 & 3

Session 15
Endocrine system disorders
2
Bioscience Department
Session Learning Outcomes

At the end of the session, you should be able to:

- Describe the function and role of the adrenal glands
- Describe the presentation, diagnosis and treatment of cortical hypofunction
- Describe the presentation, diagnosis and treatment of cortical and medullary hyperfunction
- Describe the clinical presentation of adrenal tumours
- Outline the aetiology, clinical presentation, diagnosis and treatment of hypopituitarism
- Detail the presentation and management of pituitary tumours, diabetes insipidus, acromegaly and hyperprolactinaemia
Session Plan

- Adrenal disease:
  - Overview of the adrenal glands
  - Cortical Hypofunction:
    - Adrenocortical insufficiency: Addison’s disease
    - Congenital adrenal hyperplasia
  - Cortical Hyperfunction:
    - Cushing’s syndrome
    - Primary Hyperaldosteronism
  - Medullary Hyperfunction:
    - Phaeochromocytoma
  - Tumours of the Medulla
  - Incidental adrenal mass
Session Plan

○ Hypothalamic and pituitary disease:
  • Overview of the hypothalamus and pituitary gland
  • Hypopituitarism
  • Pituitary tumour
  • Hyperprolactinaemia
  • Acromegaly
  • Diabetes insipidus
Overview of the Adrenal Glands
Adrenal Gland

- Situated on the upper pole of each kidney
- **Cortex:**
  - Glucocorticoids
  - Mineralocorticoids
  - Androgens
- **Medulla:**
  - Adrenaline
  - Noradrenaline

Tortora, GJ & Derrickson, B 2014, Principles of anatomy and physiology, 14th edn, John Wiley & Sons, Hoboken, NJ.
Adrenal Gland: Structure and Function

# Adrenal Diseases

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
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<tbody>
<tr>
<td><strong>Hormone excess</strong></td>
<td></td>
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<tr>
<td>Non-ACTH-dependent</td>
<td>ACTH-dependent</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Cushing’s syndrome</td>
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<tr>
<td>Primary hyperaldosteronism</td>
<td>syndrome</td>
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<tr>
<td>Phaeochromocytoma</td>
<td>Secondary hyperaldosteronism</td>
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<tr>
<td><strong>Hormone deficiency</strong></td>
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<tr>
<td>Addison’s disease</td>
<td>Hypopituitarism</td>
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<tr>
<td>Congenital adrenal hyperplasia</td>
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<tr>
<td><strong>Hormone hypersensitivity</strong></td>
<td></td>
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<tr>
<td>11 β-hydroxysteroid dehydrogenase type 2</td>
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<tr>
<td>deficiency</td>
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<tr>
<td>deficiency</td>
<td></td>
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<tr>
<td>Liddle’s syndrome</td>
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<tr>
<td><strong>Hormone resistance</strong></td>
<td></td>
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<tr>
<td>Pseudohypoaldosteronism</td>
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<tr>
<td>Glucocorticoid resistance</td>
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<tr>
<td>syndrome</td>
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<tr>
<td><strong>Non-functioning tumours</strong></td>
<td></td>
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<tr>
<td>Adenoma</td>
<td></td>
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<tr>
<td>Carcinoma (usually functioning)</td>
<td></td>
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<tr>
<td>Metastatic tumours</td>
<td></td>
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</tbody>
</table>

Cortical Hypofunction:
Adrenocortical Insufficiency

- **Definition:** It is an adrenal cortex hypo function resulting mainly due to inadequate secretion of cortisol and/or aldosterone.

- **Aetiology:**
  - **Secondary (↓ACTH):**
    - Withdrawal of suppressive glucocorticoid therapy
    - Hypothalamic or pituitary disease
  - **Primary (↑ACTH):**
    - Addison’s disease
    - Corticosteroid biosynthetic enzyme defects
      - Congenital adrenal hyperplasias
      - Drugs
Addison's disease

- **Definition:** It is a primary adrenocortical insufficiency resulting from partial destruction of the adrenal cortex, leading to adrenal cortex hormone deficiencies.

- **Aetiology:**
  - **Common causes:**
    - Autoimmune
    - Tuberculosis
    - HIV/AIDS
    - Metastatic carcinoma
    - Bilateral adrenalectomy
  - **Rare causes:**
    - Lymphoma
    - Intra-adrenal haemorrhage
    - Amyloidosis
    - Haemochromatosis
Addison’s disease

<table>
<thead>
<tr>
<th>Clinical Features:</th>
<th>Glucocorticoid insufficiency</th>
<th>Mineralocorticoid insufficiency</th>
<th>ACTH excess</th>
<th>Adrenal androgen insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss, anorexia</td>
<td>Hypotension</td>
<td>Pigmentation of:</td>
<td>Decreased</td>
<td></td>
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<tr>
<td>Malaise, weakness</td>
<td>Shock</td>
<td>Sun-exposed areas</td>
<td>body hair</td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Hyponatraemia (depletional)</td>
<td>Pressure areas</td>
<td>and loss of</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea or constipation</td>
<td>Hyperkalaemia</td>
<td>(e.g. elbows, knees)</td>
<td>libido,</td>
<td></td>
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<tr>
<td>Postural hypotension</td>
<td></td>
<td>Palmar creases, knuckles</td>
<td>especially in</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td>Mucous membranes</td>
<td>female</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td></td>
<td>Conjunctivae</td>
<td></td>
<td></td>
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<tr>
<td>Hyponatraemia (dilutional)</td>
<td></td>
<td>Recent scars</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td></td>
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</tr>
</tbody>
</table>
Addison’s disease
Addison’s disease

- Diagnosis:
  - Random hormone assessment: Plasma cortisol, renin, aldosterone
  - Short ACTH stimulation test
  - Electrolyte measurements: Na+, K+
  - Adrenal autoantibodies
  - Imaging of the adrenal glands
  - HIV test
Addison’s disease

- **Management:**
  - Glucocorticoid replacement therapy
  - Mineralocorticoid therapy (not always)
  - Adrenal androgen replacement (in women)
  - Regular schedule for meals and exercise
  - Medical alert bracelet

- **Complications:**
  - Adrenal crisis
  - Vitiligo
Adrenal crisis

- Definition: It is a life-threatening situation arising upon exposure to even a minor illness or stress if Addison’s disease is the underlying problem in a person.

- Clinical features:
  - Nausea
  - Vomiting
  - Muscular weakness
  - Hypotension
  - Dehydration
  - Vascular collapse
Adrenal crisis

Management:

- The *five Ss* of management:
  - Salt replacement
  - Sugar (dextrose) replacement
  - Steroid replacement
  - Support of physiologic functioning
  - Search for and treat the underlying cause
- Glucocorticoid replacement
- Mineralocorticoid therapy
Congenital Adrenal Hyperplasia

- **Definition:** It is a congenital disorder caused by an autosomal recessive trait leading to a deficiency of any of the enzymes necessary for the synthesis of cortisol.

- **Clinical features:**
  - Features of glucocorticoid and mineralocorticoid deficiency and androgen excess
  - Features of cortisol insufficiency and/or ACTH and androgen excess

- **Management:**
  - Glucocorticoid replacement
  - Anti-androgen therapy
Cortical Hyperfunction
Cushing’s Syndrome

- **Definition:** It refers to the manifestations of hypercortisolism from any cause.

### Aetiology:

<table>
<thead>
<tr>
<th>ACTH dependent</th>
<th>Non-ACTH dependent</th>
<th>Pseudo-Cushing’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary adenoma secreting ACTH</td>
<td>Adrenal adenoma or carcinoma</td>
<td>Alcohol excess</td>
</tr>
<tr>
<td>Ectopic ACTH syndrome</td>
<td>Iatrogenic (excess glucocorticoid therapy)</td>
<td>Primary obesity</td>
</tr>
<tr>
<td>ACTH therapy</td>
<td></td>
<td>Major depressive illness</td>
</tr>
</tbody>
</table>
Cushing’s Syndrome

Clinical features:

- Moon face
- Thinning of hair
- Truncal obesity
- Acne
- Facial plethora
- Buffalo hump
- Hirsutism or thinning hair
- Blue-red striae

- Menstrual irregularities
- Poor wound healing
- Osteoporosis
- Hyperglycaemia
- Muscle wasting
- Bruising
- Psychosis
- Hyperpigmentation
- Fluid retention
Cushing’s Syndrome

- Hair thinning
- Hirsutism
- Acne
- Plethora
- Moon face
- Peptic ulcer
- Loss of height and back pain from compression fracture
- Hyperglycaemia
- Menstrual disturbance
- May have exuberant callus with fractures
- Osteoporosis
- Tendency to infections with poor wound healing and little inflammatory response
- Psychosis
- Cataracts
- Mild exophthalmos
- Hypertension
- Centripetal obesity
- Striae
- Decreased skin thickness
- Wasting and weakness of proximal thigh muscles
- Bruising

Cushing’s Syndrome

○ Diagnosis:
  • To establish Cushing’s syndrome
    – 24 hours urinary free cortisol
    – low-dose/overnight dexamethasone suppression test
    – Late-night salivary cortisol
  • To define its cause
    – Plasma ACTH
    – Adrenal imaging with CT
    – Pituitary MRI
    – Corticotrophin-releasing hormone test
    – high-dose dexamethasone suppression test
    – CT/MRI thorax and abdomen
Cushing’s Syndrome

Management:

- Transsphenoidal removal of a pituitary adenoma or a hemihypophysectomy
- Cortisol replacement therapy
- Pituitary radiation therapy
- Unilateral or bilateral adrenalectomy
- Surgical removal of ectopic ACTH-producing tumors
- Pharmacologic agents that block steroid synthesis
**Primary Hyperaldosteronism**

- **Definition:** It is an intrinsic abnormality of adrenal glands resulting in aldosterone excess.

- **Aetiology:**
  - Adrenal adenoma secreting aldosterone (Conn’s syndrome)
  - Idiopathic bilateral adrenal hyperplasia
  - Glucocorticoid-suppressible hyperaldosteronism (rare)

- **Clinical features:**
  - Usually asymptomatic
  - Na+ retention or K+ loss
  - Oedema
  - Muscle weakness
  - Polyuria
  - Occasional tetany
Primary Hyperaldosteronism

○ Diagnosis:
  • Random blood biochemistry: serum K+, Na+
  • Plasma renin and aldosterone
  • Imaging: CT/MRI

○ Management:
  • Mineralocorticoid receptor antagonists
  • Unilateral adrenalectomy

Adrenal adenoma: The tumour is ‘canary yellow’ because of intracellular lipid accumulation.

Medullary Hyperfunction
Phaeochromocytoma

- Definition: It is a Rare neuro-endocrine tumour that secrete catecholamines (adrenaline, noradrenaline).

- Clinical features:
  - Hypertension
  - Paroxysms of:
    - Pallor
    - Palpitations, sweating
    - Headache
    - Anxiety
  - Abdominal pain, vomiting
  - Constipation
  - Weight loss
  - Glucose intolerance
Phaeochromocytoma

- **Diagnosis:**
  - Urinary catecholamines
  - CT/MRI abdomen

- **Management:**
  - Surgery
  - Radio/chemo therapy
Tumours of the Medulla
Incidental adrenal mass
Neuroblastoma

- Definition: It is a malignant tumour derived from the nerveoblasts. It secretes dopamine and catecholamines.

- Clinical features:
  - Hutchinson’s syndrome - bone metastasis with anaemia, limping and irritability due to bone pain
  - Pepper’s syndrome - liver with hepatomegaly
  - Rapid enlargement of the abdomen
  - Fatigue
  - Loss of appetite
  - Fever
  - Joint pain

- Management: Surgery
Incidental Adrenal Mass

- **Definition:** It is a mass lesion found unexpectedly in an adrenal gland by an imaging procedure done for other reasons.

- **Clinical features:**
  - Most are asymptomatic
  - Clinical signs and symptoms of
    - Glucocorticoid excess
    - Mineralcorticoid excess - Conn’s syndrome
    - Catecholamine excess
    - Androgen excess in women

- **Diagnosis:**
  - MRI and CT scan

- **Management:**
  - Surgery
Overview of the Hypothalamus and Pituitary Gland
Pituitary Gland

- Secretes many hormones:
  - Human Growth hormone (hGH)
  - Prolactin (PL)
  - Adrenocorticotrophic hormone (ACTH)
  - Thyroid-stimulating hormone (TSH)
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)
  - Melanocyte-stimulating hormone (MSH)
  - Oxytocin (OT) – from Posterior Pituitary
  - Antidiuretic hormone (ADH) – from Posterior Pituitary

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# Hypothalamic - Pituitary Axis

<table>
<thead>
<tr>
<th>Anterior Pituitary cells</th>
<th>Hormone from pituitary</th>
<th>Regulatory hormone from hypothalamus</th>
<th>Target organ</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatotrophs</td>
<td>hGH</td>
<td>GHRH, GHIH</td>
<td>Bones, muscles, liver, body</td>
<td>Growth and development</td>
</tr>
<tr>
<td>Lactotrophs</td>
<td>PRL</td>
<td>PRH, PIH</td>
<td>Mammary Glands</td>
<td>Production of milk and lactation</td>
</tr>
<tr>
<td>Thyrotrophs</td>
<td>TSH</td>
<td>TRH</td>
<td>Thyroid Gland</td>
<td>Release of thyroid hormones T3/T4</td>
</tr>
<tr>
<td>Corticotrophs</td>
<td>MSH</td>
<td>CRH</td>
<td>Skin</td>
<td>Pigmentation</td>
</tr>
<tr>
<td></td>
<td>ACTH</td>
<td>CRH</td>
<td>Adrenal cortex</td>
<td>Release of corticoids</td>
</tr>
</tbody>
</table>
| Gonadotrophs             | FSH                    | GnRH                                 | Gonads | M: Sperm production and release of testosterone  
|                          | LH                     | GnRH                                 | Gonads | F: follicular development and release of oestrogen/progesterone |
Pituitary Diseases
Hypopituitarism

- **Definition:** It describes combined deficiency of any of the anterior pituitary hormones.

- **Aetiology:**
  - **Structural:**
    - Pituitary tumours
    - Meningiomas
  - **Inflammatory:**
    - Sarcoidosis
    - Haemochromatosis
    - TB
  - **Congenital deficiencies:**
    - GNRH
    - GHRH
    - TRH
    - CRH
  - **Functional:**
    - Chronic illness
    - Excessive exercise.
Hypopituitarism

Clinical features:
- Growth hormone
  - Lethargy
- Gonadotrophins
  - Lethargy
  - Loss of libido
  - Hair loss
  - Amenorrhoea
- ACTH
  - Lethargy
  - Postural hypotension
  - Pallor
  - Hair loss
- TSH
  - Lethargy
- Vasopressin (ADH) (usually post-surgical)
  - Thirst and polyuria
Hypopituitarism

- Diagnosis:
  - Tests to identify Pituitary hormone deficiency
  - MRI or CT scan of brain
  - Further investigations to exclude infectious or infiltrative causes

Hypopituitarism

- Management:
  - Acutely ill patients:
    - Similar to adrenocortical insufficiency
  - Chronic condition:
    - Chronic hormone replacement
    - Specific treatment for the underlying causes
Pituitary Tumours

- Definition: Mass lesions found in or around the pituitary gland.

- Clinical features:
  - Headache
  - Visual field defects
  - Optic atrophy
  - Acute-onset hypopituitarism
Pituitary Tumours

○ Diagnosis:
  • MRI and CT scan
  • Biopsy

○ Management:
  • Surgery
  • Radiotherapy
  • Treat associated hypopituitarism
Hyperprolactinaemia

- Definition: Hyperprolactinaemia is a common abnormality which usually presents with hypogonadism and/or galactorrhoea.

- Aetiology:
  - Physiological: Stress, Pregnancy, Exercise, A baby crying
  - Drugs: Antipsychotics, Antidepressants, Dopamine depleting drugs
  - Pathological: Primary hypothyroidism, Pituitary tumours, Renal failure
Hyperprolactinaemia

○ Clinical features:
  • Women
    – Secondary amenorrhoea
    – Anovulation
    – Infertility
  • Men
    – Decreased libido
    – Reduced shaving
    – Lethargy
Hyperprolactinaemia

- **Diagnosis:**
  - Prolactin levels
  - Gonad function tests
  - $T_4$ and TSH levels

- **Management:**
  - Treat underlying cause
  - Dopamine agonist therapy
Acromegaly

- Definition: Acromegaly is caused by growth hormone (GH) secretion after the epiphyseal closure in adults from a pituitary tumour, usually a macroadenoma, and carries an approximate two-fold excess mortality when untreated.

- Clinical features:
  - Headache
  - Sweating
  - Features of pituitary tumours
  - Coarse facial features
  - Thick skin
  - Enlarged organs
  - Hypertension
  - Cardiomyopathy
  - Excessive sweating
Acromegaly

- Headache
- Enlargement of lips, nose and tongue
- Cardiomyopathy
  - Cardiovascular disease (2–3 × 1)
- Hypertension
- Enlargement of liver
- Enlargement of hands
  - Arthropathy
  - Carpal tunnel syndrome
- Skull growth – prominent supraorbital ridges with large frontal sinuses
- Prognathism (growth of lower jaw)
- Increased sweating
- Thickened skin
- IGT (25%)/type 2 diabetes (10%)
- Colonic cancer (2–3 × 1)
- Myopathy
- Enlargement of feet
  - Increased heel pad thickness

Acromegaly

Images from:
Tortora, GJ & Derrickson, B 2014, Principles of anatomy and physiology, 14th edn, John Wiley & Sons, Hoboken, NJ.
http://trialx.com/curetalk/wp-content/blogs.dir/7/files/2011/05/diseases/Acromegaly_And_Gigantism-1.jpg
http://www.helpfulhealthtips.com/acromegaly/
Acromegaly

- **Diagnosis:**
  - GH levels during oral glucose test
  - Pituitary function tests
  - Prolactin levels
  - Colonoscopy for colonic neoplasms screening

- **Management:**
  - Surgery
  - Radiotherapy
  - Drugs to lower GH secretion
Diabetes Insipidus

- Definition: It is characterised by the persistent excretion of excessive quantities of dilute urine and by thirst due to deficient or unresponsive ADH.

- Classification:
  - Cranial diabetes insipidus: There is deficient production of ADH by the hypothalamus
  - Nephrogenic diabetes insipidus: the renal tubules are unresponsive to ADH.
Diabetes Insipidus

- Aetiology:
  - Cranial
    - Structural hypothalamic or high stalk lesion
    - Idiopathic
    - Genetic defect of enzymes for biosynthesis of ADH
  - Nephrogenic
    - Genetic defect for ADH receptors
    - Metabolic abnormality
    - Drug therapy
    - Poisoning
    - Chronic kidney disease
Diabetes Insipidus

- Clinical features:
  - **Polydipsia**
  - **Polyuria** (5–20 L or more of urine in 24 hours)
  - Conscious patients with intact thirst mechanism:
    - Maintain adequate fluid intake
  - Unconscious patients/ with damage to the hypothalamic thirst centre:
    - Diabetes insipidus is potentially lethal.
Diabetes Insipidus

- **Diagnosis:**
  - Water deprivation test

- **Management:**
  - Demopressin
  - Thyozide diuretics, amiloride
  - NSAIDs
Reading and Resources

- Crowley LV, 2012, *An Introduction to Human Diseases – Pathology and Pathophysiology Correlations*, 9th edn, Jones and Bartlett Learning
Reading and Resources

- Mosby’s dictionary of medicine, nursing and health professions 2013, 9th edn, Elsevier, St. Louis, MO.
- VanMeter, KC & Hubert, RJ 2014, *Gould's pathophysiology for the health professions*, 5th edn, Elsevier, St Louis, MO.
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