The Endocrine System Blueprint

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Disclosure

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OBJECTIVES

• Review functions of endocrine organs, metabolism of their hormones and their effects on the body

• Review and understand the pathogenesis and pathophysiology of diseases of pituitary, thyroid, parathyroid, adrenal, pancreas, testes and ovaries.

• Review most current diagnostic testing and pharmacotherapy for endocrine related disorders
Disorders of the Parathyroid and Thyroid Glands
Primary Hyperparathyroidism

- Excess PTH secretion from one or more of the parathyroid glands leading to hypercalcemia (calcium >11 mg/dL)
- A single benign parathyroid adenoma is found in 80-90% of cases.
- Parathyroid carcinoma is extremely rare
Clinical Presentation

- 80% of cases of hyperparathyroidism are asymptomatic.
- Fatigue
- Nocturia and polyuria: hypercalcemia inhibits ADH secretion
- Constipation
- Neuromuscular dysfunction: muscle weakness
- Neuropsychiatric disturbance: depression, personality disorders

- Mnemonic:
  - Bones
  - Stones
  - Abdominal moans
  - Psychic groans
  - hyper tones
Skeletal Complications

- Severe bone pain
- Fractures of the bones
- Osteoporosis
- Kidney stones
Diagnostic Testing

Laboratory Findings
- Elevated PTH >60 pg/mL
- Elevated serum calcium level >10.5 mg/dL
- Serum phosphorus is low (<2.5 mg/dL)
- Elevated 24 hour urine calcium creatinine ratio >300 mg/day

Imaging
- TC-99m Sestamibi scan
  - Gold standard
  - Sensitivity and Specificity is >95%
Treatment

- Parathyroidectomy
  - Is the definitive treatment for primary hyperparathyroidism

- Complications:
  - Damage to the recurrent laryngeal nerve
Hypoparathyroidism

• Inappropriately low secretion of PTH
  • Hallmark:
    • Low PTH
    • Low calcium level (hypocalcemia)
    • Elevated phosphorus (hyperphosphatemia)
    • Low 24 hour urinary calcium excretion
    • Low 1,25(OH)D3
Clinical Presentation

- Paresthesia
  - Numbness and tingling of the extremities
  - Carpopedal spasms
- Life threatening laryngeal stridor due to laryngeal spasm
- CNS manifestations
  - Seizures
  - Confusion
  - Irritability
  - Worsening dementia in adults
Surgical Hypoparathyroidism

- The most common cause of hypoparathyroidism is due to removal or destruction of the PTH glands.
- Patient’s with Grave’s disease undergoing thyroidectomy are most likely to experience hypocalcemia
- Tetany ensues 1-2 days postoperatively
Diagnostic Testing

- Low serum calcium or iCa
- Low PTH level
- High phosphorus level

- Electrocardiography
  - Prolongation of the QTc interval and shortening of the RR interval
Treatment of hypocalcemia

- IV calcium
  - Calcium gluconate
- Oral calcium
  - Calcium carbonate 1-3 grams/day
- Vitamin D supplementation
  - Vitamin D2 (ergocalciferol)
  - Vitamin D3 (cholecalciferol)
  - Calcitriol (1,25 (OH)2D)
The Thyroid Gland

- Hormones secreted by the thyroid gland:
  - Thyroxine (T4)
  - Triiodothyronine (T3)
  - Thyroid-binding globulin (TBG)
  - Plasma calcitonin [tumor maker for medullary carcinoma of the thyroid (MTC)]
## Antibodies to the Thyroid Gland

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Description</th>
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<tbody>
<tr>
<td>Thyroid peroxidase antibody (TPO)</td>
<td>Is a marker for autoimmune hypothyroidism (Hashimoto’s Thyroiditis)</td>
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<tr>
<td>Thyroglobulin antibody (ATA)</td>
<td>Is a marker for autoimmune hypothyroidism</td>
</tr>
<tr>
<td>TSH receptor antibody</td>
<td>Thyroid stimulating immunoglobulin (TSI)</td>
</tr>
<tr>
<td></td>
<td>• Always positive in Grave’s disease</td>
</tr>
<tr>
<td></td>
<td>• Best markers for diagnosis of autoimmune hyperthyroidism (Grave’s)</td>
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Grave’s Disease

- Is the most common form of hyperthyroidism
- Females are affected about 5 times more than males
- Peak incidence is 20-40 years
  - Consists of the following features
    1. Thyrotoxicosis
    2. Goiter
    3. Ophthalmopathy (exophthalmos)
    4. Dermopathy (pretibial myxedema)
Pathogenesis of Grave’s Disease

- Autoimmune disorder
  - Thyroid stimulating Immunoglobulin (TSI) also known as thyroid-stimulating antibody (TSAb):
    - binds to the TSH receptor and mimics the effects of TSH
Symptoms of Hyperthyroidism

- Heat intolerance with increased sweating
- Weight loss with increased appetite
- Anxiety, irritability
- Chest palpitations
- Oligomenorrhea
- Fatigue and weakness
- Brisk reflexes
- Tremors of the hands
- Lid lag, stare
- Atrial fibrillation
- Sinus tachycardia
- Hair loss
- Muscle weakness and wasting
Diagnostic Testing

- Plasma TSH: suppressed or low
- Free T4, T4 and T3: elevated
- Thyroglobulin: elevated
- Thyroid receptor Ab or TSI: always positive
- Thyroid peroxidase Ab: positive or negative
Treatment

- Radioactive Iodine therapy (I131)
  - Is the preferred treatment of choice for almost all patients with Grave’s disease
  - Cannot be used during pregnancy or during lactation
  - It has proven to be safe and does not cause fertility problems or cancer.
  - Complications: Hypothyroidism
# Oral Medication

<table>
<thead>
<tr>
<th>Propylthiouracil (PTU)</th>
<th>Methimazole (Tapazole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• It blocks peripheral conversion of T4 into T3</td>
<td>• Inhibits thyroid hormones synthesis</td>
</tr>
<tr>
<td>• 250 - 400 mg every 6 hours</td>
<td>• 10-20 mg daily</td>
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<tr>
<td>• Is the preferred treatment during pregnancy in the first trimester</td>
<td>• Should be used after the first trimester to prevent aplasia cutis (congenital absence of the skin)</td>
</tr>
<tr>
<td></td>
<td>• Agranulocytosis</td>
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<td></td>
<td>• Rash</td>
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Thyroid Surgery

• Is preferred if the patient has failed thyroid radioactive iodine treatment in two different occasions.

• Complications:
  • Hypoparathyroidism
  • Injury to recurrent laryngeal nerve causing permanent vocal cord paralysis
Thyroid Storm

- Acute exacerbation of thyrotoxicosis
- Is a life threatening condition
  - Malignant fever associated with flushing and sweating
  - Marked tachycardia with atrial fibrillation
  - Elevated blood pressure
  - Heart failure
  - Delirium and coma
Management of thyroid storm

- Admission to ICU
- Propranolol 1 to 2 mg IV every 5-10 minutes
- PTU or Methimazole rectal suppository if person cannot swallow
- Potassium Iodine solution: 10 drops twice daily
- Hydrocortisone 50 mg IV
- Cooling blankets
- Acetaminophen
- IV fluids
- Oxygen, diuretics and digoxin for heart failure
- Plasmapheresis or peritoneal dialysis to remove high levels of circulating thyroid hormones
Other forms of Hyperthyroidism

- Toxic Adenoma
  - Hyper secretes T3 and T4
  - Start our as small nodule and slowly increases in size
  - Benign in nature
  - Ophthalmopathy is never present
Hashimoto’s Thyroiditis

- Is the most common cause of acquired hypothyroidism in the USA
- The thyroid gland is damaged by cell-mediated immunity: TPO and ATA
- More common in women
- Increases in prevalence with age
- Diffuse goiter without tenderness
Hypothyroidism

Children and Adolescents

• Signs and Symptoms
  • Retarded growth and short stature
  • Decreased school performance due to lack of concentration.
  • Tiredness and fatigue
  • Excessive sleep time
  • Irregular menstrual cycles

Adults

• Signs and Symptoms
  • Easy fatigability
  • Cold sensitivity
  • Weight gain
  • Constipation
  • Menorrhagia
  • Muscle cramp
Diagnostic Testing

- Elevated TSH
- Low free T4
- Thyroid peroxidase antibody (TPO) always positive in autoimmune thyroiditis
- Thyroglobulin antibody (ATA) may be positive or normal in autoimmune thyroiditis
Treatment

- Synthroid or Levothyroxine

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose (mcg/kg/day)</th>
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<tr>
<td>0-3 months</td>
<td>10-15</td>
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<tr>
<td>4-6 months</td>
<td>8-10</td>
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<tr>
<td>7-12 months</td>
<td>6-8</td>
</tr>
<tr>
<td>1-5 years</td>
<td>5-6</td>
</tr>
<tr>
<td>6-12 years</td>
<td>4-5</td>
</tr>
<tr>
<td>&gt; 12 years/puberty incomplete</td>
<td>2-3</td>
</tr>
<tr>
<td>&gt; 12 years/puberty complete</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Subacute Thyroiditis

- Also known as de Quervain’s or granulomatous thyroiditis:
  - Painful and tender goiter
  - Transient hyperthyroidism followed by transient hypothyroidism
  - It usually occurs after an upper respiratory tract infection

- Treatment:
  - Beta blocker if hyperthyroid symptoms are moderate
  - NSAIDS for the thyroid pain
  - Corticosteroids may be used in severe cases
  - Transient hypothyroidism can be treated with Synthroid
Neoplastic Disease of the Parathyroid Glands

• Multiple Endocrine Neoplasia 1 (MEN1)
• Defect in the gene encoding tumor suppressor menin
  • Parathyroid adenoma
  • Pancreatic tumors
  • Pituitary adenomas
• Autosomal dominant
• Hypercalcemia is found in 95% of cases and is the most predominant symptom.
MEN2A and MEN2B

- **MEN2A**
  - Parathyroid Adenoma
  - Medullary thyroid cancer
  - Pheochromocytoma
  - Autosomal dominant
  - Defects in the RET proto-oncogene

- **MEN2B**
  - Medullary thyroid carcinoma
  - Pheochromocytomas
  - Mucosal Neuromas
  - Marfanoid body habitus
Thyroid Nodules

- Thyroid nodules are common and the incidence increases with age
- Most nodules are benign in nature
- Painless lump in the neck discovered by the physician
- Nodules <1 cm only require closed follow up.
- Nodules >1 cm require fine needle aspiration (FNA)
- Nodules >2 cm should be removed as they can become hyperplastic.
Thyroid Carcinoma

- Risk for carcinomas:
  - <20 years of age with cervical lymphadenopathy
  - History of head or neck radiation
  - Family history of medullary thyroid carcinoma or multiple endocrine neoplasia (MEN) Type 2A or 2B
  - Hard fixed fast growing nodule
  - Hoarseness due to invasion of recurrent laryngeal nerve
  - Most people have no symptoms
Papillary Carcinoma

- The most common type of thyroid cancer (80%)
- Slow growing tumor that remains localized for many years.
- Metastasizes first to cervical lymph nodes
Follicular Carcinoma

- Follicular Carcinoma
  - Accounts for 15% of thyroid tumors
  - Is more aggressive than papillary carcinoma
  - Metastasize early to lungs and bones

- Anaplastic Carcinoma
  - Rare
  - Rapidly progressive thyroid cancer
  - Poor prognosis
Anaplastic thyroid carcinoma
--Rare
--Rapidly progressive thyroid cancer
--Poor prognosis
• Medullary thyroid carcinoma (MCT)
  • Arises from C cells (parafollicular cells)
  • Secretes plasma calcitonin that is always elevated and is useful for diagnosis
  • MCT is a component of the MEN 2A and 2B
Diagnosis of thyroid carcinoma

- Most patients are asymptomatic
- TSH, free T4, T4, T3 = are always normal
- The best diagnostic procedure of choice: Fine needle aspiration (FNA)
Treatment

• Total Thyroidectomy: initial treatment

• Radioactive Iodine Ablation (Iodine 131)
  • Due to high re-occurrence of thyroid cancer, thyroid ablation is performed

• Synthroid or Levothyroxine to treat the hypothyroidism
Life long-monitoring

- Whole body scan are performed yearly until 2 scans are negative.

- Plasma thyroglobulin: a rising thyroglobulin indicates tumor recurrence

- Calcitonin: Rising calcitonin level indicates recurrence of MTC
The Adrenal Gland
Addison’s Disease

- Rare disorder
- Female to male ratio 2:1
- Diagnosis is difficult as patients can have the disease for a prolong time until a stressor precipitates an adrenal crisis.
Adrenal Crisis

- Electrolytes Abnormalities
  - ↓ sodium
  - ↑ potassium
  - ↓ chloride
  - ↓ glucose
  - ↓ bicarbonate
Diagnostic Testing

- Basal cortisol Measurements:
  - Must be drawn before 9 AM (never in the afternoon)
  - Cortisol >19 mcg/dL rules out adrenal insufficiency (5-23 mcg/dL)
  - Cortisol <3 mcg/dL suspicious for adrenal insufficiency

Adrenal antibodies are detected in 90% of patients with autoimmune adrenal insufficiency:

A) Adrenal Cortex Antibody (ACA)
B) 21-Hydroxylase Antibody (CYP21A2)

The presence of both antibodies make the diagnosis likely up to 99% in most cases.
Corticotropin Stimulation Test  
(Synthetic ACTH)

- Gold standard to establish diagnosis of adrenal primary adrenal insufficiency:
  - Draw plasma ACTH and cortisol levels
  - Give corticotropin (synthetic ACTH)
    - 250 mcg IV push (adult)
    - 1 mcg IV push (children)
  - Draw plasma cortisol at 30 and 60 minutes post corticotropin push:
    - Cortisol >18 mcg/dL = NO ADRENAL INSUFFICIENCY
Maintenance Therapy

**Children**
- Hydrocortisone (10-20 mg/m2/day) divided in 2-3 equal doses per day
  - Double the dosage during illness
- Fludrocortisone 0.05 - 0.2 mg once or twice daily. It is titrated base on renin levels and electrolytes

**Adults**
- Prednisone 4 - 7.5 mg/day
  - Double the dosage during illness
- Fludrocortisone 0.5 - 2 mg once or twice daily.
Cushing Disease

- Excessive ACTH secretion from pituitary tumor resulting in increase cortisol and androgen levels
- Accounts for 80% of cases
- Elevated ACTH and cortisol
  - can be suppressed with Dexamethasone
Ectopic ACTH Hypersecretion

- ACTH secretion from non-pituitary tumor:
  - Bronchial carcinoid
  - Small cell carcinoma
  - Prognosis is poor
- Accounts for 10% of cases
- Elevated ACTH and cortisol
  - Cannot be suppressed with Dexamethasone
Primary Adrenal Gland Tumors

Adrenal tumors:
- Adenomas: 10% of cases
- Carcinomas: rare

Elevated Cortisol level
Suppressed ACTH level
Symptoms and Signs of Cushing’s

• Obesity
  • Most common manifestation
  • Central obesity:
    • Neck = posterior fat pad
    • Trunk
    • Abdomen
    • Moon face
• Skin Changes in Cushing’s
  • Atrophy of the epidermis
  • Thinning of the skin
  • Facial plethora
  • Red to purple striae
  • Pustular acne
Diagnostic Testing

1) Dexamethasone Suppression Test
   - Dexamethasone 1 mg is given at 11 PM
   - Cortisol levels are drawn by 8 AM the next day
     - If <1.8 mcg/dL then is normal. NO Cushing!

2) 24 hour urine free Cortisol (≥2 tests)
   - >50 ug/24 hours (must be 3-4 times of the normal range)

3) Late night salivary test
   11 pm salivary radioimmunoassay if greater than 0.15 ug/dL then suspicious for Cushing's
Imaging

- MRI of the Brain to locate pituitary tumor
- MRI or CT scan of adrenal glands to locate tumor
- MRI or CT scan of the chest for ectopic ACTH producing tumor
Treatment

- Pituitary adenoma: Trans sphenoidal surgery
- Adrenal Adenoma: unilateral adrenalectomy
- Adrenal Carcinoma: unilateral adrenalectomy and mitotane therapy.
- Ectopic ACTH producing tumor: Surgery
Disorders of the Pituitary Gland
Acromegaly

- Pituitary Adenoma with excess growth hormone production:
  - Post-pubertal phase: Acromegaly
  - Pre-pubertal phase: Gigantism
- Rare disorder: 3 cases per 1 million
- Insidious resulting in a lag time between onset and diagnosis
Acromegaly: Post-pubertal phase

Gigantism: Pre-pubertal phase
Signs and Symptoms

• Increase in hat, ring or shoe size
• Headache is the second most common symptom
• Coarsen facial features:
  • Mandible more prominent: pragmatism and malocclusion
  • Macroglossia
  • Deep coarse voice due to hypertrophy of laryngeal muscles
Signs and Symptoms

Arthralgia and myalgia will be present in 30-70% of patients due to bone overgrowth

Paresthesia related to carpal tunnel syndrome

Visual disturbances
Diagnostic Testing

- IGF-1 and GH (growth hormone) levels
- Oral glucose tolerance test (OGTT)(gold standard)
  --Draw glucose and growth hormone level at base line
  --Give 75 grams of oral glucose
  --Measure glucose and growth hormone every 30 minutes for 2 hours:
    If GH level falls to <0.3 mcg/L = no acromegaly

- MRI with and without contrast
- Radiograph of the skull may show enlarged sella and thickened skull
- Echocardiography will show interventricular septum and left ventricular hypertrophy
Medications

- Somatostatin Analogs:
  - Octreotide (Sandostatin) 10 mg SC monthly
  - Lanreotide (Somaline) 60 mg SC monthly
  - Pegvisomant (Somavert) 10 mg SC daily

- Dopamine Agonists:
  - Carbegoline 0.25 - 1.0 mg twice weekly
Surgical Management

• Surgical Management is considered if pharmacological treatment fails.
  • Trans sphenoidal surgery
  • Conventional Radiation Therapy (not preferred)
  • Stereotactic radio-surgery: gamma knife

• Chemotherapy
Dwarfism

- Growth hormone deficiency
  - Most cases are idiopathic
  - Small percentage of the cases are secondary to pituitary neoplasm
    - Craniopharyngioma most common pituitary tumor associated with growth hormone deficiency