Pemphigus Vulgaris

Dr. Rasha Turky
Ass. Prof of Dermatology, Andrology and STDs
It is a severe, life-threatening, autoimmune, intraepidermal blistering disease affecting skin and mucous membranes and is characterized by acantholysis of epidermal cells.

It is a disease of adults (40-60 years).

Both sexes are equally affected.
Etiology

- It is an autoimmune disease.
- Circulating IgG autoantibodies bind to intercellular adhesion molecules (Desmogleins) between epidermal cells of skin and oral mucosa causing loss of cellular adhesion (Acantholysis) resulting in blister formation.
Clinical features

- P.V. affects skin and oral mucosa.

- The disease starts in the oral mucosa in 50%-70% of cases 6-12 months before the appearance of skin lesions.

- More than 90% of patients will develop oral lesions at some time during the course of the disease.
Skin lesions:

- Generalized flaccid bullae are seen that rupture easily leaving crusted erosions.
- The erosions heal slowly leaving hyperpigmentation.

Oral lesions:

- Bullae occur anywhere in the oral cavity.
- They rupture easily and thus intact bullae are rarely seen.
- Patients usually present with persistent large painful erosions and ulcers that heal slowly.
Dermatopathology

- The major histologic feature is **suprabasal acantholysis** “Separation of keratinocytes”.
Diagnosis

- **Biopsy:** From small bullae or erosions.

- **Tzanck smear:** Swab from the base of erosions or freshly opened blisters shows acantholytic cells.

- **Direct immunofluorescence:** of perilesional skin shows intercellular deposits of **IgG and/or C3**.

- **Indirect immunofluorescence:** Circulating IgG autoantibodies against **desmoglein 3** are detected in 80%-90% of cases.
Differential Diagnosis

- Oral lesions must be differentiated from:
  - Erosive lichen planus.
  - Behcet’s disease.
  - Oral lesions of Stevens-Johnson syndrome.
Treatment

1) Patients with oral lesions only:
   - Intralesional injection of triamicinolone acetonide 10-20mg/ml can be helpful.

2) Patients with generalized disease:
   - Patient must be hospitalized.
   - Systemic corticosteroids are given orally in a dose of 1-3 mg/kg body weight/day (Usually 120-240mg/day) until cessation of new blister formation. This is followed by gradual withdrawal of corticosteroids to the minimally effective dose.
   - Correction of water and electrolyte imbalance and prevention of secondary infection are important.
The mortality rate is 5% and it is mainly due to:

- Steroid-induced complications.
- Sepsis.
Thank You!
Sexually transmitted diseases

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Sexually Transmitted diseases are a group of infectious diseases in which the principle method of infection is sexual contact.
Syphilis

- **Causative organism:** A spirochaete known as Treponema pallidum (T.P.).
- **Incubation period:** 2-4 weeks and may be up to 90 days.
- **Mode of transmission:** Mainly by direct contact with infectious lesions.
  1. **Sexual contact** is the most common method of infection.
  2. Accidental contact e.g. medical personnel.
  3. Needle pricks and blood transfusion.
  4. Transplacental infection from infected mother to her baby.
  5. Indirect contact e.g. from WC is rare.
Classification:

A) Acquired syphilis.
B) Congenital syphilis.
A) Acquired Syphilis

It is further subdivided into 4 stages:

1) Primary syphilis.
2) Secondary syphilis.
3) Latent syphilis.
4) Tertiary syphilis.
1) Primary syphilis

Clinical features:

- The primary lesion of syphilis is known as **chancre**.
- It appears at the site of entry of T.P.
- 90% of chancres are seen at or near the **genital area**.
- 10% of chancres are **extra genital** and have been described on almost every part of the body e.g. on the lips, tongue, tonsils, breast, fingers … etc
- Typical chancre is: solitary, painless, indurated, well-defined, circular or oval and exudes clear serum.
- Regional lymph nodes become enlarged one week after appearance of chancre. They are discreet, firm to rubbery in consistency, neither painful nor tender and freely mobile.
Natural course of primary syphilis:

- Even without treatment, chancre undergoes spontaneous healing within 2-4 weeks leaving a thin scar.
- 75% of patients enter phase of latency i.e. complete freedom from symptoms and signs in the presence of +ve serological tests. It lasts from 2 weeks to 6 months.
- 25% of patients develop manifestations of secondary syphilis while the chancre is still present.
2) Secondary syphilis

- The lesions appear 1-6 months after the appearance of the primary lesion.
- Any organ of the body can be affected, although skin and mucous membranes are mainly affected.
Clinical manifestations of 2ry syphilis:

1) Skin lesions.
2) Mucous membrane lesions.
3) Lymphadenopathy.
4) Alopecia.
5) Generalized constitutional symptoms e.g. fever, headache, malaise, anorexia weight loss.
1- Skin lesions.
- The lesions may be macular, papular or maculopapular. However, the commonest and most characteristic is the **papule**.
- Skin rashes appear as generalized, symptomless, rosy macules and papules.

2- Mucous membrane lesions:
- Mucous membrane lesions **“Mucous patches”**: appear as shallow white erosions on mucosal surfaces e.g. oral mucosa, palate, pharynx, larynx, vagina or urethra.
- After sometime, the mucous patches show confluence giving **“Snail-track ulcers”**.
Natural course of secondary syphilis:

- It may consist of a single episode lasting for several weeks or a series of recurrent episodes.
- In untreated cases, secondary manifestations cease to occur 2-3 years after infection.
3) Tertiary Syphilis

Clinical manifestations of tertiary syphilis include:

1- Benign late syphilis: *Gumma*.
2- Cardiovascular syphilis.
3- Neurosyphilis.
1. Benign Late Syphilis “Gumma”

- It affects mainly: skin, mucous membranes, subcutaneous tissue & submucosal tissue.

- It may also affect: muscles, bones and sometimes internal organs.
I- Skin lesions

The lesions are: firm, painless with a characteristic arciform or serpiginous outline. Healing occurs with thin, atrophic, tissue-paper like scar.
II. Mucosal lesions of the mouth, nose & throat

- **Gumma** may originate in the submucosa of the palate, pharynx, larynx or nasal septum. It begins as painless swelling that may breakdown to give an ulcer with a characteristic **punched-out** appearance.

- Perforation of the palate, destruction of the uvula, laryngeal stenosis and nasal deformity may occur.

- The tongue may be involved with deep interstitial glossitis causing **“macroglossia”** and latter on **“deep fissured tongue”**.

- **Leukoplakia** may occur especially on the tongue, inner aspect of cheeks and lips. 50% of these lesions undergo malignant change.
2- Cardiovascular syphilis:

- It is the result of *endarteritis obliterans* of the vasa vasorum supplying the major vessels e.g. aorta and coronary arteries. Damage to the wall of these vessels results in: Aortitis, aortic aneurysm, aortic incompetence and angina pectoris.
3- **Neurosyphilis:**

- It is the result of inflammation of meninges and endarteritis obliterans of the vasa vasorum supplying blood vessels of the brain and/or spinal cord.

- **Clinical presentations include:**
  1- Syphilitic meningitis: Localized or diffuse.
  2- Tabes dorsalis: Due to damage of the dorsal nerve roots.
  3- General paralysis of the insane: Due to degeneration of the brain itself.
B) Congenital Syphilis

**Mode of infection:** Trans-placental.

**Clinical manifestations:** are similar to the 2ry stage of syphilis in adults.

1) **General symptoms & signs:**
- Failure to thrive.
- Thrombocytopenia, bleeding and anaemia (due to affection of blood forming organs).
- Pneumonia or gastroentritis.
2) **Skin lesions:**

- Generalized macular or maculopapular rash.
- Bullous lesions may occur.
- Condylomata lata may be seen.
- Skin lesions have a predilection for certain areas: face, around mouth, napkin area, the palms and soles.
3) **Mucous membrane lesions:**

- Rhinitis and nasal snuffles are common.
- Destructive changes of nasal supportive structures causing perforation of the nasal septum and depression of the nasal bridge “*Saddle-shaped nose*”.
- **Mucous patches** may occur in the pharynx and larynx causing hoarse cry.
4) **Bone lesions:**
- Epiphysitis is common ulna and radius.
- Bilateral osteomyelitis of the inner aspect of the tibia is pathognomonic.

5) **Other organs:**
- There may be generalized lymphadenopathy, hepatospleno-megally, meningitis, choroidoretinitis or nephrotic syndrome.
Stigmata of congenital syphilis

- These are the residual manifestations of congenital syphilis throughout life.

- They include:
  1) Dental changes.
  2) Other stigmata.
1) **Dental changes:**

Due to invasion of the tooth germ with T.P. causing endarteritis. These changes include:

a) **Hutchinson’s teeth:** Affect central incisors, which become notched and the cutting edge is narrower than the gingival edge.

b) **Moon’s molar:** Affect molar teeth where the 4 cusps tend to be packed together in the center instead of being at the corners.
2) Other stigmata:

- Interstitial keratitis.
- Perforation of the hard palate
- Saddle nose.
- 8th nerve deafness
- Rhagades: Linear lesions around the mouth and anus.
- Sabre tibia.
Treatment of Syphilis

- Penicillin, being the cheapest and most effective is the drug of choice.

- The ones available are:
  - **Procaine penicillin**: Single injection is effective for 24 hrs.
  - **Benzathine penicillin G**: Single injection is effective for 2 weeks.
For those allergic to penicillin, one of the following regimens may be used:

1) **Tetracycline HCl**: 500mg/6hs for 15 days (Early syphilis) or 30 days (Late syphilis)

2) **Doxycycline**: 100mg/8hs (Early syphilis) or 21 days (Late syphilis)

3) **Erythromycin**: 500mg/6hs for 15 days (Early syphilis) or 30 days (Late syphilis)
Thank You!
Thyroid Regulation

HYPOTHALAMUS - TRH

ANT. PITUITARY - TSH

TSH -R

THYROID T4 and T3

PLASMA T4 + FT4

PLASMA T3 + FT3

TISSUES FT4 to FT3, rT3
HYPERTHYROIDISM
Where to look for Thyroid?
Clinical Exam of Thyroid
Clinical Exam of Thyroid
Clinical Exam of Thyroid
Thyromegaly

Thyroid Cartilage (Adam’s Apple)

Enlarged Left Lobe Thyroid
Causes of Hyperthyroidism

1. Graves Disease – Diffuse Toxic Goiter
2. Plummer’s Disease – Toxic MNG
3. Toxic phase of Sub Acute Thyroiditis - SAT
4. Toxic Single Adenoma – STA
5. Pituitary Tumours – excess TSH
6. Molar pregnancy & Choriocarcinoma (↑↑ βHCG)
7. Metastatic thyroid cancers (functioning)
8. Struma Ovari (Dermoid and Ovarian tumours)
9. Thyrotoxicosis Factitia ; INF, Amiodarone, SSRIs
Clinical Features

1. Those that occur with any type of thyrotoxicosis

2. Those that are specific to Graves disease

3. Non specific changes of hyper metabolism
Common Symptoms

1. Nervousness
2. Anxiety
3. Increased perspiration
4. Heat intolerance
5. Tremor
6. Hyperactivity
7. Palpitations
8. Weight loss despite increased appetite
9. Reduction in menstrual flow or oligomenorrhea
Common Signs

1. Hyperactivity, Hyper kinesis
2. Sinus tachycardia or atrial arrhythmia, AF, CHF
3. Systolic hypertension, wide pulse pressure
4. Warm, moist, soft and smooth skin- warm handshake
5. Excessive perspiration, palmar erythema, Onycholysis
6. Lid lag and stare (sympathetic over activity)
7. Fine tremor of out stretched hands – format's sign
8. Large muscle weakness, Diarrhea, Gynecomastia
Specific to Graves Disease

1. Diffuse painless and firm enlargement of thyroid gland
2. Thyroid bruit is audible with the bell of stethoscope
3. Ophthalmopathy – Eye manifestations – 50% of cases
   - Sand in eyes, periorbital edema, conjunctival edema (chemosis), poor lid closure, extraocular muscle dysfunction, diplopia, pain on eye movements and proptosis.
4. Dermoacropathy – Skin/limb manifestations – 20% of cases
   - Deposition of glycosaminoglycans in the dermis of the lower leg – non pitting edema, associated with erythema and thickening of the skin, without pain or pruritus - called (pre tibial myxedema)
Diagnosis

1. Typical clinical presentation
2. Markedly suppressed TSH (<0.05 µIU/mL)
3. Elevated FT$_4$ and FT$_3$ (Markedly in Graves)
4. Thyroid antibodies – by Elisa – anti-TPO, TSI
5. ECG to demonstrate cardiac manifestations
6. Nuclear Scintigraphy to differentiate the causes
Treatment Options

1. Symptom relief medications

2. Anti Thyroid Drugs – ATD
   - Methimazole, Carbimazole
   - Propylthiouracil (PTU)


4. Thyroidectomy – Subtotal or Total

5. NSAIDs and Corticosteroids – for SAT
Classification of Hypothyroidism

A. Primary

1. Enlarged Thyroid
   - Hashimoto’s (65%)
   - Iodine Deficiency (25%)
   - Drug-induced (Lithium)
   - Dysharmonogenesis

2. Normal Thyroid
   - Spontaneous Atrophic

Primary contd..

3. Post Ablative
   - Permanent
   - Transient
   - Sub-clinical

4. Congenital

B. Secondary / Central

   Pituitary/ hypothalamic
Multi system effects - Hypothyroidism

General
• Lethargy, Somnalence
• Weight gain, Goitre
• Cold Intolerance

Cardiovascular
• Bradycardia, Angina
• CHF, Pericardial Effusion
• HyperlipIdemia, Xanthelsma

Haematological
Iron def. Anaemia,
Normo cytic /chromic Anaemia

Reproductive system
• Infertility, Menorrhagia
• Impotence, Inc. Prolactin

Neuromuscular
• Aches and pains
• Muscle stiffness
• Carpel tunnel syndrome
• Deafness, Hoarseness
• Cerebellar ataxia
• Delayed DTR, Myotonia
• Depression, Psychosis

Gastro-intestinal
• Constipation, Ileus, Ascites

Dermatological
• Dry flaky skin and hair
• Myxoedema, Malar flushes
• Vitiligo, Carotenimia, Alopecia
Clinical Signs of Hypothyroidism

- Coarse Hair; Dry cool and pale skin
- Goitre (not in all cases), Hoarseness of voice
- Non-pitting oedema (myxoedema)
- Puffiness of eyes and face
- Delayed relaxation of DTR
- Slow hoarse speech and slow movements
- Thinning of lateral 1/3 of eye brows
- Bradycardia, pericardial effusion
Hormone replacement
Many Causes, One Treatment

• **Goal**: Normalize TSH level regardless of cause of hypothyroidism

• **Treatment**: Once daily dosing with Levothyroxine sodium (1.6µg/kg/day) this comes to 100 mcg per day

• **Monitor TSH levels** at 6 to 8 weeks, after initiation of therapy or dosage change
PARATHYROID GLAND PHYSIOLOGY
• 99% calcium of our body is in the crystalline form in the skeleton and teeth
• Of the remaining 1%
  0.9% intracellular
  less than 0.1% in the ECF
• The extracellular fluid calcium concentration is about 9.4 mg/dl
Calcium in Plasma and Interstitial Fluid

- 41% of the calcium is bound with plasma proteins (non-diffusible)
- 9% bound with anionic substances (citrate, phosphate (diffusible, non-ionized))
- Remaining 50% calcium is both diffusible and ionized
Hypocalcemia (low blood calcium)

- Fall in free calcium results in over excitability of nerves and muscles
- Decrease in free calcium increases neuronal sodium permeability with resultant influx of sodium moving the resting potential closer to threshold
Tetany

- Hypocalcemia causes tetany
- At plasma calcium ion concentration about 50% below normal the peripheral nerve fibers become so excitable that they begin to discharge spontaneously
- Tetany usually occurs at calcium conc of 6 mg/dl from normal value of 9 mg/dl
Hypercalcemia (elevated blood calcium)

- Depresses neuro-muscular excitability
- Depressive effects begin to appear at calcium concentration of 12mg/dl (constipation, poor appetite, decreased QT interval)
HORMONAL REGULATION OF CALCIUM AND PHOSPHATE HOMEOSTASIS

• PTH
• Vitamin D
• Calcitonin
PARATHYROID GLANDS

- Four glands located on the posterior surface of the thyroid gland
- Derived from the 3\text{rd} and 4\text{th} pharangeal pouches
- Chief cells secrete the polypeptide hormone PTH
TARGET ORGANS FOR PTH

- Bone
- Kidney
Hyperparathyroidism
Low circulating serum calcium concentrations stimulate the parathyroid glands to secrete PTH, which mobilizes calcium from bones by osteoclastic stimulation. PTH also stimulates the kidneys to reabsorb calcium and to convert 25-hydroxyvitamin D3 (produced in the liver) to the active form, 1,25-dihydroxyvitamin D3, which stimulates GI calcium absorption. High serum calcium concentrations have a negative feedback effect on PTH secretion.
Hypercalcemia

I. Hyperparathyroidism
   - Primary hyperparathyroidism
   Tertiary HPT

II. Malignancy-related

III. Endocrine diseases:
   Hyperthyroidism. Addisonian crisis. Pheochromocytoma

IV. Granulomatous diseases: Sarcoidosis. T.B.

IV. Iatrogenic:
   Excessive intake of Vit D or calcium
   - Rx with lithium
   - Thiazide diuretics

V. Associated with renal failure
   - Severe secondary hyperparathyroidism
   - Aluminum intoxication

VI. Familial hypocalcuric hypercalcemia
   - Milk-alkali syndrome

**Primary hyperparathyroidism and cancer account for 90% of cases of hypercalcemia**
Primary Hyperparathyroidism

PHPT

Incidence: 0.1-0.3%. 1 case per 1000 men and 2-3 cases per 1000 women. 25/100000 population

- Incidence increases above age 40
- Most patients with sporadic PHPT are postmenopausal women with an average age of 55 years

Etiology:
- A solitary parathyroid adenoma (83%)
- Multiple adenomas (6%)
- Hyperplasia 10%
- Carcinoma 1%
Primary HPT: Clinical Features

- Symptomatic:
- Classical pentad of symptoms (Kid. stones, painful bones
  - Osteitis fibrosa cystica
  - Nephrolithiasis
  - Pathologic fractures
  - Neuromuscular disease
  - Life-threatening hypercalcemia
  - DU. pancreatitis

- Asymptomatic: Hypercalmic
  - Fatigue, muscle weakness & ache
  - Depression
  - Polydipsia, Polyuria
  - Anorexia, dyspepsia wt loss, Constipation
  - SOB, HT
## Biochemical features of prim HPT

<table>
<thead>
<tr>
<th>Serum tests</th>
<th>Alteration</th>
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<tbody>
<tr>
<td>Calcium</td>
<td>Increased</td>
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<tr>
<td>Intact PTH</td>
<td>Increased (&gt;0.5mg/L)</td>
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<tr>
<td>Phosphate</td>
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</tbody>
</table>
Surgical Candidacy

• Symptomatic primary HPT
  – Serum calcium greater than 1mg/dL above the upper limit of the reference range (>11mg%)
  – 24 hour urine calcium greater than 400 mg
  – Creatinine clearance reduced by more than 30% compared with age-matched subjects
  – Marked reduced Bone density
  – Age under 50
  – Urinary calculi
  – Neuromuscular presentation

Asymptomatic cases
  follow up serum calcium level
Medical Management of Acute Hypercalcemia

- Adequate hydration
- Intravenous Bisphosphonates
- Prednisolone
- Calcitonin
- Oral phosphate
Hypocalcemia
Causes of hypocalcemia

- Hypoparathyriodism
- pseudohypoparathyriodism
- Hypovitamiosis D, resistance to vitamin D
- Chronic renal failure
- Miscellaneous: Acute pancreatitis
Symptoms and signs of hypocalcemia

- Neuromuscular irritability
- Paresthesias
- Laryngospasm / Bronchospasm
- Tetany
- Seizures
- Chvostek sign
- Trousseau sign
- Prolonged QTc time on ECG
ASSESSMENT TIP

Eliciting Chvostek’s sign

Begin by telling the patient to relax his facial muscles. Then stand directly in front of him, and tap the facial nerve either just anterior to the ear-lobe and below the zygomatic arch or between the zygomatic arch and the corner of his mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of hypocalcemia.
Trousseau sign:
(very uncomfortable and painful)

• A blood pressure cuff is inflated to a pressure above the patients systolic level.
• Pressure is continued for several minutes.
• Carpopedal spasm:
  * flexion at the wrist
  * flexion at the MP joints
  * extension of the IP joints
  * adduction thumbs/fingers
Management

1. Dependent on the underlying cause and severity
2. Administration of calcium alone is only transiently effective
3. Mild asymptomatic cases: Often adequate to increase dietary calcium by 1000 mg/day
4. Symptomatic: Treat immediately
Treatment of hypocalcaemia

Symptomatic hypocalcaemia
– IV Calcium should only be given with close monitoring
– Should be on cardiac monitor
– Mix with NaCl or 5 % D/W (not bicarbonate/lactate containing solutions)

Risks
– Tissue necrosis/calcification if extravasates
– Calcium can inhibit sinus node → bradycardia + arrest
  • Stop infusion if bradycardia develops
– Avoid complete correction of hypocalcaemia
– With acidosis and ↓ S-Ca – give Ca before correcting acidosis
– If ↓ Mg is cause of ↓ S-Ca – treat and correct hypomagnesaemia
Adrenal Insufficiency

UNC Internal Medicine Morning Report
June 28, 2010
Edward L. Barnes, MD
Adrenal Insufficiency

• Primary Adrenal Insufficiency is also known as Addison’s Disease in honor of Dr. Thomas Addison

• Born in April 1793, at Long Benton, Newcastle-upon-Tyne and died on June 29 1860, at 15 Wellington Villas, Brighton

• Dr. Addison is also credited with the discovery of Pernicious Anemia
Introduction

• Adrenocorticotropic Hormone (ACTH) is the major factor in the secretion of cortisol and androgenic steroids by the adrenal cortex

• ACTH secretion is regulated as a balance between the stimulatory effects of CRH (mediated by the CNS) and the negative feedback mediated by circulating levels of glucocorticoids
Adrenal Insufficiency

• Arises when cortisol levels are not sufficient to meet the needs of the body
• Cortisol aids in maintaining vascular tone, hepatic gluconeogenesis, and in maintaining glycogen
• Inadequate cortisol in times of stress can lead to hypotension, shock, and hypoglycemia
Adrenal Insufficiency

- Mineralocorticoid deficiency typically leads to renal wasting of sodium, retention of potassium, and reduced intravascular volume.
Primary Adrenal Insufficiency

- Most commonly is of an autoimmune etiology, resulting from chronic destruction of the adrenal cortex
- Typical histologic feature is lymphocytic infiltration
- Antibodies to adrenal cortical antigens are present early in the disease process
- Patients with autoimmune adrenal disease are more likely to have polyglandular autoimmune systems causing deficiency of other endocrine glands
Primary Adrenal Insufficiency

• Several Other Mechanisms Exist:
  – Bilateral adrenal hemorrhage
  – Infection: Tuberculosis, CMV, Histoplasmosis
  – Metastatic Disease
  – Deposition Diseases: Hemochromatosis, Amyloidosis, Sarcoidosis
  – Drug Induced: Ketoconazole, Etomidate, Rifampin, Anticonvulsants
  – Congenital Adrenal Hyperplasias
Secondary Adrenal Insufficiency

• Caused by pituitary failure of ACTH secretion

• Etiologies include:
  – any cause of primary or secondary hypopituitarism
  – Exogenous Glucocorticoid Therapy
  – Megestrol, which has some glucocorticoid therapy
Clinical Presentation

• Acute adrenal insufficiency (Adrenal Crisis) should be expected in any patient acute, unexplained volume depletion and shock
• Hyperkalemia, acidosis, and hypoglycemia may also be accompanying
Clinical Presentation

- Chronic insufficiency typically develops more insidiously
- Symptoms may include weakness, weight loss, nausea, vomiting, anorexia, and postural hypotension
- Increased skin pigmentation can be seen with primary adrenal insufficiency secondary to melanocyte stimulating activity associated with ACTH
- Hyponatremia and Hyperkalemia may develop secondary to a lack of aldosterone
Clinical Presentation

• Secondary Adrenal Insufficiency may present with evidence of adrenal insufficiency as well as other evidence of hypopituitarism
Differential Diagnosis

• Acute Adrenal insufficiency
  – Various conditions can cause hypotension and or shock

• Chronic Adrenal Insufficiency
  – Chronic Starvation (anorexia nervosa)
  – Gastrointestinal Disease secondary to inflammation or malignancy
  – Other causes of hyperpigmentation including drug exposures
  – Other causes of fatigue and malaise
Diagnostic Workup

- Baseline Cortisol and ACTH levels should be obtained in the early morning
  - A morning cortisol level of <3 µg/dL is virtually diagnostic
  - A level of <10 µg/dL is highly suspicious
  - A level of >18 µg/dL should rule out Adrenal Insufficiency except in the setting of a critically ill patient
Diagnostic Workup

– Cosyntropin Stimulation Test
  • Measure morning cortisol level (pre-test level)
  • Administer 1 µg dose Cosyntropin
  • Measure a second cortisol level 1 hour after Cosyntropin administration
  • Normal response demonstrates a level of greater than 20 µg/dL after cosyntropin
  • Patients with both primary and secondary adrenal insufficiency will not demonstrate appropriate response

– Patients with primary insufficiency will fail to respond to repeated administrations, however patients with secondary insufficiency may show an increased response to repeated testing/stimulation
Diagnostic Workup

– Further determination of primary vs. secondary adrenal insufficiency will be based upon ACTH level
– High ACTH level expected in primary insufficiency
Treatment: Acute Adrenal Insufficiency

- Treat Acute Adrenal Insufficiency with Hydrocortisone 50-100 mg IV q8 hrs
- In addition, volume resuscitate with Normal Saline
Treatment: Chronic Adrenal Insufficiency

- Hydrocortisone 20-30 mg po daily
  - Typically divide dose 2/3 in am, 1/3 in pm
- May use Prednisone 5 mg po daily instead
- Fludrocortisone 0.05-0.1 mg po qam
  - Not necessary in patients with secondary adrenal insufficiency
- Provide instruction for periods of acute illness or increased stress
Thyroid Regulation

HYPOTHALAMUS - TRH

ANT. PITUITARY - TSH

TSH -R

THYROID T4 and T3

PLASMA T4 + FT4

PLASMA T3 + FT3

TISSUES FT4 to FT3, rT3
HYPERTHYROIDISM
Where to look for Thyroid?
Clinical Exam of Thyroid
Clinical Exam of Thyroid
Clinical Exam of Thyroid
Thyromegaly

![Image showing Thyroid Cartilage (Adam’s Apple) and Enlarged Left Lobe Thyroid]
Causes of Hyperthyroidism

1. Graves Disease – Diffuse Toxic Goiter
2. Plummer’s Disease – Toxic MNG
3. Toxic phase of Sub Acute Thyroiditis - SAT
4. Toxic Single Adenoma – STA
5. Pituitary Tumours – excess TSH
6. Molar pregnancy & Choriocarcinoma (↑↑ βHCG)
7. Metastatic thyroid cancers (functioning)
8. Struma Ovari (Dermoid and Ovarian tumours)
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2. Those that are specific to Graves disease

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Common Symptoms

1. Nervousness
2. Anxiety
3. Increased perspiration
4. Heat intolerance
5. Tremor
6. Hyperactivity
7. Palpitations
8. Weight loss despite increased appetite
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2. Sinus tachycardia or atrial arrhythmia, AF, CHF
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Specific to Graves Disease

1. Diffuse painless and firm enlargement of thyroid gland
2. Thyroid bruit is audible with the bell of stethoscope
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2. Markedly suppressed TSH (<0.05 µIU/mL)
3. Elevated FT$_4$ and FT$_3$ (Markedly in Graves)
4. Thyroid antibodies – by Elisa – anti-TPO, TSI
5. ECG to demonstrate cardiac manifestations
6. Nuclear Scintigraphy to differentiate the causes
Treatment Options

1. Symptom relief medications
2. Anti Thyroid Drugs – ATD
   - Methimazole, Carbimazole
   - Propylthiouracil (PTU)
4. Thyroidectomy – Subtotal or Total
5. NSAIDs and Corticosteroids – for SAT
HYPOTHYROIDISM
Classification of Hypothyroidism

A. Primary
1. Enlarged Thyroid
   - Hashimoto’s (65%)
   - Iodine Deficiency (25%)
   - Drug-induced (Lithium)
   - Dysharmonogenesis
2. Normal Thyroid
   - Spontaneous Atrophic

Primary contd..
3. Post Ablative
   - Permanent
   - Transient
   - Sub-clinical

4. Congenital

B. Secondary / Central

Pituitary/ hypothalamic
Multi system effects - Hypothyroidism

General
- Lethargy, Somnalence
- Weight gain, Goitre
- Cold Intolerance

Cardiovascular
- Bradycardia, Angina
- CHF, Pericardial Effusion
- HyperlipIdemia, Xanthelsma

Haematological
- Iron def. Anaemia,
- Normo cytic /chromic Anaemia

Reproductive system
- Infertility, Menorrhagia
- Impotence, Inc. Prolactin

Neuromuscular
- Aches and pains
- Muscle stiffness
- Carpel tunnel syndrome
- Deafness, Hoarseness
- Cerebellar ataxia
- Delayed DTR, Myotonia
- Depression, Psychosis

Gastro-intestinal
- Constipation, Ileus, Ascites

Dermatological
- Dry flaky skin and hair
- Myxoedema, Malar flushes
- Vitiligo, Carotenimia, Alopecia
Clinical Signs of Hypothyroidism

- Coarse Hair; Dry cool and pale skin
- Goitre (not in all cases), Hoarseness of voice
- Non-pitting oedema (myxoedema)
- Puffiness of eyes and face
- Delayed relaxation of DTR
- Slow hoarse speech and slow movements
- Thinning of lateral 1/3 of eye brows
- Bradycardia, pericardial effusion
Hormone replacement
Many Causes, One Treatment

• **Goal:** Normalize TSH level regardless of cause of hypothyroidism

• **Treatment:** Once daily dosing with Levothyroxine sodium (1.6µg/kg/day) this comes to 100 mcg per day

• **Monitor TSH levels** at 6 to 8 weeks, after initiation of therapy or dosage change
• 99% calcium of our body is in the crystalline form in the skeleton and teeth
• Of the remaining 1%
  0.9% intracellular
  less than 0.1% in the ECF
• The extracellular fluid calcium concentration is about 9.4 mg/dl
Calcium in Plasma and Interstitial Fluid

- 41% of the calcium is bound with plasma proteins (non-diffusible)
- 9% bound with anionic substances (citrate, phosphate (diffusible, non-ionized)
- Remaining 50% calcium is both diffusible and ionized
Hypocalcemia (low blood calcium)

- Fall in free calcium results in over excitability of nerves and muscles
- Decrease in free calcium increases neuronal sodium permeability with resultant influx of sodium moving the resting potential closer to threshold
Tetany

- Hypocalcemia causes tetany
- At plasma calcium ion concentration about 50% below normal the peripheral nerve fibers become so excitable that they begin to discharge spontaneously
- Tetany usually occurs at calcium conc of 6 mg/dl from normal value of 9 mg/dl
Hypercalcemia (elevated blood calcium)

- Depresses neuro-muscular excitability
- Depressive effects begin to appear at calcium concentration of 12mg/dl (constipation, poor appetite, decreased QT interval)
HORMONAL REGULATION OF CALCIUM AND PHOSPHATE HOMEOSTASIS

- PTH
- Vitamin D
- Calcitonin
PARATHYROID GLANDS

- Four glands located on the posterior surface of the thyroid gland
- Derived from the 3\textsuperscript{rd} and 4\textsuperscript{th} pharangeal pouches
- Chief cells secrete the polypeptide hormone PTH
Thyroid gland

Parathyroid gland (located on posterior side of the thyroid gland)

Chief cell
Oxyphil cell
Red blood cell
TARGET ORGANS FOR PTH

- Bone
- Kidney
Hyperparathyroidism
Low circulating serum calcium concentrations stimulate the parathyroid glands to secrete PTH, which mobilizes calcium from bones by osteoclastic stimulation. PTH also stimulates the kidneys to reabsorb calcium and to convert 25-hydroxyvitamin D3 (produced in the liver) to the active form, 1,25-dihydroxyvitamin D3, which stimulates GI calcium absorption. High serum calcium concentrations have a negative feedback effect on PTH secretion.
I. Hyperparathyroidism
   - Primary hyperparathyroidism
   Tertiary HPT
II. Malignancy-related
   
III. Endocrine diseases:
   Hyperthyroidism. Addisonian crisis. Pheochromocytoma
IV. Granulomatous diseases: Sarcoidosis. T.B.
IV. Iatrogenic:
   Excessive intake of Vit D or calcium
   - Rx with lithium
   - Thiazide diuretics
V. Associated with renal failure
   - Severe secondary hyperparathyroidism
   - Aluminum intoxication
VI. Familial hypocalcric hypercalcemia
   - Milk-alkali syndrome

**Primary hyperparathyroidism and cancer account for 90% of cases of hypercalcemia**
Primary Hyperparathyroidism

PHPT

Incidence: 0.1-0.3%. 1 case per 1000 men and 2-3 cases per 1000 women. 25/100000 population

- Incidence increases above age 40
- Most patients with sporadic PHPT are postmenopausal women with an average age of 55 years

Etiology: a solitary parathyroid adenoma (83%)

- Multiple adenomas (6%)

- Hyperplasia 10%
- Carcinoma 1%
Primary HPT: Clinical Features

- **Symptomatic:**
  - Classical pentad of symptoms (Kid.stones, painful bones
    - Osteitis fibrosa cystica
    - Nephrolithiasis
    - Pathologic fractures
    - Neuromuscular disease
    - Life-threatening hypercalcemia
    - **DU.pancreatitis**

- **Asymptomatic:** Hypercalmic
  - Fatigue, muscle weakness & ache
  - Depression
  - Polydipsia, Polyuria
  - Anorexia, dyspepsia wt loss, Constipation
  - SOB, HT
## Biochemical features of prim HPT

<table>
<thead>
<tr>
<th>Serum tests</th>
<th>Alteration</th>
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<tbody>
<tr>
<td>Calcium</td>
<td>Increased</td>
</tr>
<tr>
<td>Intact PTH</td>
<td>Increased (&gt;0.5mg/L)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>↓</td>
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</tbody>
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Surgical Candidacy

- **Symptomatic primary HPT**
  - Serum calcium greater than 1mg/dL above the upper limit of the reference range (>11mg%)
  - 24 hour urine calcium greater than 400 mg
  - Creatinine clearance reduced by more than 30% compared with age-matched subjects
  - Marked reduced Bone density
  - Age under 50
  - Urinary calculi
  - Neuromuscular presentation

**Asymptomatic cases**
  - follow up serum calcium level
Medical Management of Acute Hypercalcemia

• Adequate hydration
• Intravenous Bisphosphonates
• Prednisolone
• Calcitonin
• Oral phosphate
Hypocalcemia
Causes of hypocalcemia

• Hypoparathyriodism
• pseudohypoparathyriodism
• Hypovitamiosis D, resistance to vitamin D
• Chronic renal failure
• Miscellaneous: Acute pancreatitis
Symptoms and signs of hypocalcemia

• Neuromuscular irritability
• Paresthesias
• Laryngospasm / Bronchospasm
• Tetany
• Seizures
• Chvostek sign
• Trousseau sign
• Prolonged QTc time on ECG
Eliciting Chvostek’s sign

Begin by telling the patient to relax his facial muscles. Then stand directly in front of him, and tap the facial nerve either just anterior to the earlobe and below the zygomatic arch or between the zygomatic arch and the corner of his mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of hypocalcemia.
Trousseau sign:
(very uncomfortable and painful)

• A blood pressure cuff is inflated to a pressure above the patients systolic level.
• Pressure is continued for several minutes.
• Carpopedal spasm:
  * flexion at the wrist
  * flexion at the MP joints
  * extension of the IP joints
  * adduction thumbs/fingers
Management

1. Dependent on the underlying cause and severity
2. Administration of calcium alone is only transiently effective
3. Mild asymptomatic cases: Often adequate to increase dietary calcium by 1000 mg/day
4. Symptomatic: Treat immediately
Treatment of hypocalcaemia

Symptomatic hypocalcaemia

– IV Calcium should only be given with close monitoring
– Should be on cardiac monitor
– Mix with NaCl or 5 % D/W (not bicarbonate/lactate containing solutions)

Risks

– Tissue necrosis/calcification if extravasates
– Calcium can inhibit sinus node → bradycardia + arrest
  • Stop infusion if bradycardia develops
– Avoid complete correction of hypocalcaemia
– With acidosis and ↓ S-Ca – give Ca before correcting acidosis
– If ↓ Mg is cause of ↓ S-Ca – treat and correct hypomagnesaemia
Adrenal Insufficiency

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Edward L. Barnes, MD
Adrenal Insufficiency

• Primary Adrenal Insufficiency is also known as Addison’s Disease in honor of Dr. Thomas Addison

• Born in April 1793, at Long Benton, Newcastle-upon-Tyne and died on June 29 1860, at 15 Wellington Villas, Brighton

• Dr. Addison is also credited with the discovery of Pernicious Anemia
Introduction

- Adrenocorticotropic Hormone (ACTH) is the major factor in the secretion of cortisol and androgenic steroids by the adrenal cortex
- ACTH secretion is regulated as a balance between the stimulatory effects of CRH (mediated by the CNS) and the negative feedback mediated by circulating levels of glucocorticoids
Adrenal Insufficiency

• Arises when cortisol levels are not sufficient to meet the needs of the body
• Cortisol aids in maintaining vascular tone, hepatic gluconeogenesis, and in maintaining glycogen
• Inadequate cortisol in times of stress can lead to hypotension, shock, and hypoglycemia
Adrenal Insufficiency

• Mineralocorticoid deficiency typically leads to renal wasting of sodium, retention of potassium, and reduced intravascular volume
Primary Adrenal Insufficiency

- Most commonly is of an autoimmune etiology, resulting from chronic destruction of the adrenal cortex
- Typical histologic feature is lymphocytic infiltration
- Antibodies to adrenal cortical antigens are present early in the disease process
- Patients with autoimmune adrenal disease are more likely to have polyglandular autoimmune systems causing deficiency of other endocrine glands
Primary Adrenal Insufficiency

• Several Other Mechanisms Exist:
  – Bilateral adrenal hemorrhage
  – Infection: Tuberculosis, CMV, Histoplasmosis
  – Metastatic Disease
  – Deposition Diseases: Hemochromatosis, Amyloidosis, Sarcoidosis
  – Drug Induced: Ketoconazole, Etomidate, Rifampin, Anticonvulsants
  – Congenital Adrenal Hyperplasias
Secondary Adrenal Insufficiency

• Caused by pituitary failure of ACTH secretion

• Etiologies include:
  – any cause of primary or secondary hypopituitarism
  – Exogenous Glucocorticoid Therapy
  – Megestrol, which has some glucocorticoid therapy
Clinical Presentation

• Acute adrenal insufficiency (Adrenal Crisis) should be expected in any patient acute, unexplained volume depletion and shock

• Hyperkalemia, acidosis, and hypoglycemia may also be accompanying
Clinical Presentation

- Chronic insufficiency typically develops more insidiously
- Symptoms may include weakness, weight loss, nausea, vomiting, anorexia, and postural hypotension
- Increased skin pigmentation can be seen with primary adrenal insufficiency secondary to melanocyte stimulating activity associated with ACTH
- Hyponatremia and Hyperkalemia may develop secondary to a lack of aldosterone
Clinical Presentation

• Secondary Adrenal Insufficiency may present with evidence of adrenal insufficiency as well as other evidence of hypopituitarism
Differential Diagnosis

- Acute Adrenal insufficiency
  - Various conditions can cause hypotension and or shock
- Chronic Adrenal Insufficiency
  - Chronic Starvation (anorexia nervosa)
  - Gastrointestinal Disease secondary to inflammation or malignancy
  - Other causes of hyperpigmentation including drug exposures
  - Other causes of fatigue and malaise
Diagnostic Workup

• Baseline Cortisol and ACTH levels should be obtained in the early morning
  – A morning cortisol level of <3 µg/dL is virtually diagnostic
  – A level of <10 µg/dL is highly suspicious
  – A level of >18 µg/dL should rule out Adrenal Insufficiency except in the setting of a critically ill patient
Diagnostic Workup

– Cosyntropin Stimulation Test
  • Measure morning cortisol level (pre-test level)
  • Administer 1 μg dose Cosyntropin
  • Measure a second cortisol level 1 hour after Cosyntropin administration
  • Normal response demonstrates a level of greater than 20 μg/dL after cosyntropin
  • Patients with both primary and secondary adrenal insufficiency will not demonstrate appropriate response

– Patients with primary insufficiency will fail to respond to repeated administrations, however patients with secondary insufficiency may show an increased response to repeated testing/stimulation
Diagnostic Workup

- Further determination of primary vs. secondary adrenal insufficiency will be based upon ACTH level
- High ACTH level expected in primary insufficiency
Treatment: Acute Adrenal Insufficiency

- Treat Acute Adrenal Insufficiency with Hydrocortisone 50-100 mg IV q8 hrs
- In addition, volume resuscitate with Normal Saline
Treatment: Chronic Adrenal Insufficiency

- Hydrocortisone 20-30 mg po daily
  - Typically divide dose 2/3 in am, 1/3 in pm
- May use Prednisone 5 mg po daily instead
- Fludrocortisone 0.05-0.1 mg po qam
  - Not necessary in patients with secondary adrenal insufficiency
- Provide instruction for periods of acute illness or increased stress