Pituitary & Adrenal Disorders

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Clinical Case 1

66-year-old female with diabetes for 16 years, on metformin, Januvia and glipizide, but not under control. The family is not happy with previous care. Physicians are busy with their computer and not listening to the patient.

- History
- Exam
- Endocrine causes
- Further tests

ACROMEGALY

Persistent hypersecretion of GH

↓

Stimulates hepatic secretion of IGF-1

↓

Clinical findings in acromegaly

Acromegaly previously considered rare: 30-70 individuals per million

Recent report: 1000 individuals per million

In type 2 diabetes: Prevalence of 480 per million

Clinical Features

- Enlarged jaw (macrognathia)
- Hands – glove size increased and rings tight
- Feet – shoe size increased
- Face – coarse, enlarged nose, frontal bones and jaw

ACROMEGALY IN A GIANTESS

FIG. 1.—Side view showing shape of face, rounding of the shoulders and enlargement of the hand.

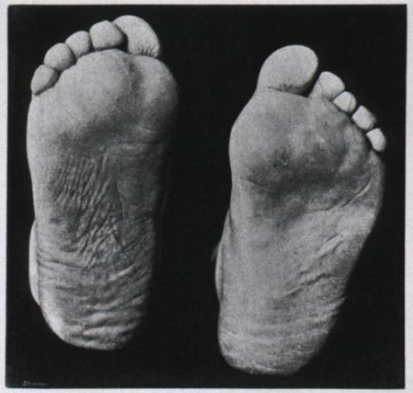


FIG. 5.—Feet, showing the broad, flat shape of the soles, which are thickly padded with fat

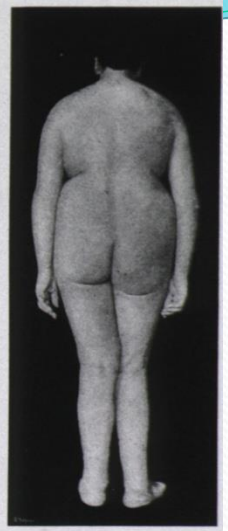


FIG. 4.—Back view showing general configuration of the body.

FIG. 2.—Front view showing the patient's enormous size, and the enlargement of the hands and feet. The patient who is standing by the side of the giantess was a woman of average height.

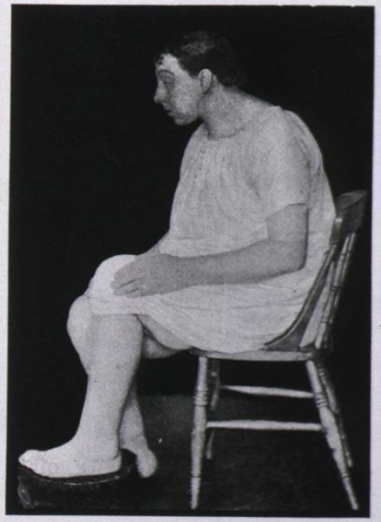
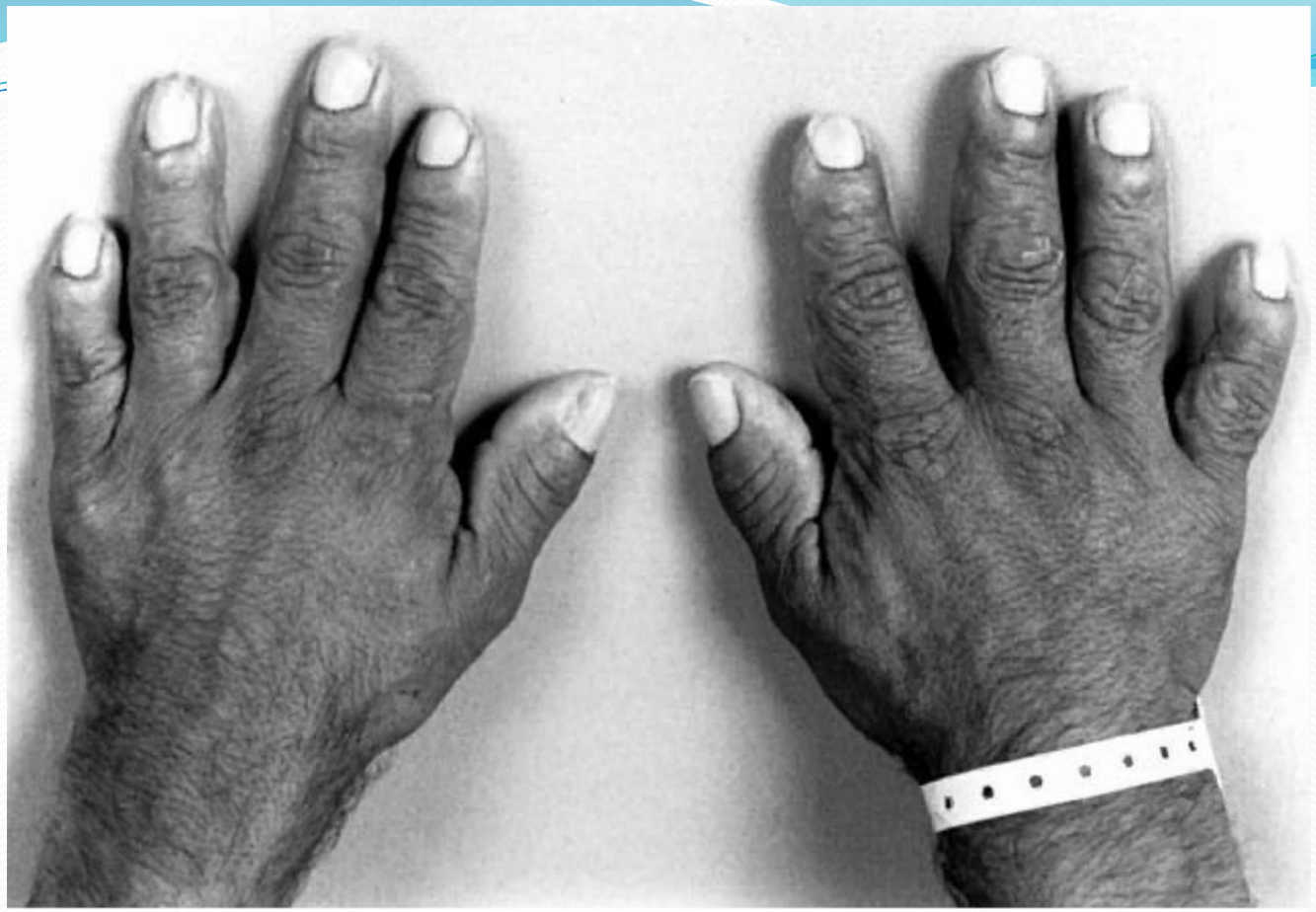


FIG. 3.—Profile view showing shape of face and enlargement of the hand and foot.



Markedly increased soft tissue bulk and blunt fingers in a middle-aged man with acromegaly. (Reproduced, with permission, from Greenspan FS, Strewler GJ [editors]. Basic & Clinical Endocrinology, 5th ed. Originally published by Appleton & Lange. Copyright © 1997 by The McGraw-Hill Companies, Inc.)

- Cardiovascular disease
- Sleep apnea
- Type 2 diabetes
- Arthropathies
- Carpal tunnel syndrome
- Pituitary tumor – leads to headache and increased visual field loss

Diagnostic Evaluation

- Clinical suspicion
- Pituitary adenoma in more than 95%
- Biochemical tests

Biochemical Tests

Serum insulin-like growth factor

IGF-1; if normal, not acromegaly

IGF-1

Conditions Associated With Low Serum IGF-1

- Hypothyroidism
- Malnutrition
- Poorly controlled type 1 diabetes
- Liver failure
- Renal failure
- Oral estrogen use
- Difference in the calibration standards for the assay

Growth Hormone

- Random test not useful
- Pulsatile, diurnal
- Fasting, sleep, exercise, stress
- Clearance rapid plasma half life 20 minutes
- High in liver disease, malnutrition, uncontrolled diabetes

OGTT With GH

- The most specific test
- In normal serum GH falls to 1 ng/mL or less within 2 hours after ingestion of 75 gm glucose
- In acromegaly > 2 ng/mL in 85%

Other Tests

- TRH test (500 mcg) IV
  - GH rises by 50% at 20-30 minutes (not in normal)
- L-Dopa 500 mg p.o.
  - Reduces GH by 50%
  - Raises GH in normal
- Serum IGFBP-3
  - GH dependent
  - Elevated in acromegaly, but not always

Pituitary function

- Mostly gonadotropin decreased
- Increased prolactin in 30%
- TSH and ACTH deficiency less common

Causes of acromegaly

Primary GH excess

GH-cell adenoma

Mixed GH-cell and PRL-cell adenoma

Mammosomatotroph-cell adenoma

Plurihormonal adenoma

GH-cell carcinoma

Familial syndromes

Multiple endocrine neoplasia type 1 (GH-cell adenoma)

Familial acromegaly

McCune-Albright syndrome (rarely adenoma)

Carney's syndrome

GH excess (ectopic or iatrogenic)

Pancreatic islet-cell tumor

Lymphoma

Iatrogenic

GHRH excess

Central ectopic (<1 percent)

Hypothalamic hamartoma, choristoma, ganglioneuroma

Peripheral ectopic (1 percent)

Bronchial carcinoid, pancreatic islet-cell tumor, small cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma

Other Tests

- Abdominal and chest imaging
- Catheterization studies
- If ectopic GHRH suspected
- May account for 0.5% of cases
- Measure serum GHRH

Acromegaly – Goals of Therapy

- Lower IGF-1 to reference range for age and gender
- Serum growth hormone less than 1 ng/mL after glucose load
- IGF-1 is a better test than growth hormone
- Normal growth hormone secretion is not often achieved

Treatment

- Transsphenoidal surgery for micro-adenomas, resectable macro-adenomas, and macroadenoma causing impairment in vision
- If IGF-1 is not normal, use long-acting somatostatin analog

Transsphenoidal Surgery

- Of microadenoma – normal in 80-90%
- IGF-1 level falls slowly over 7 days to several months
- Growth hormone falls to normal in 1-2 hours

Medical Therapy

- When adenoma is not fully resectable
- Adenoma does not abut optic chiasma
- Unfit for surgery
- The patient does not want surgery

Complications of Surgery

- Long-term deficiency of pituitary hormones up to 70%
- Worse if treated with surgery and irradiation
- Other complications 8%

  DI 2%

  CSF rhinorrhea 2%

  Meningitis 2%

  More in macroadenomas

Medical Therapy

- Somatostatin analogs once monthly

  Octreotide (sandostatin LAR)

  Lanreotide (somatuline depot)

- Inhibit growth hormone secretion by binding to receptors

- May shrink pituitary adenoma

Medical Therapy of Acromegaly

Somatostatin analogs inhibit GH secretion

- Octreotide IM 20-40 mg monthly
- Landreotide depot 60-120 mg every 4-6 weeks
- Pasireotide LAR
  - Better biochemical control but hyperglycemia increased
- Oral Octreotide not available ?

Side Effects of Somatostatin Analogs

- Few
- Nausea, abdominal discomfort, bloating, loose stools, fat malabsorption

Octreotide

- Reduces postprandial gallbladder contractility and delays gallbladder emptying
- 25% of patients develop asymptomatic gallstones

Efficacy

- Normal IGF-1 40-75%
  - If combined with cabergoline, may be better
- Clinical improvement in soft tissue swelling
  - Carpal tunnel
  - Snoring
  - Sleep apnea
  - Left ventricular function
- Adenoma size decreased by 20-30% in 30% of patients

Surgical Cure Rate

- Normal IGF-1
  - growth hormone less than 1 ng after glucose load
- Cure rate
  - 80-90% in microadenoma
  - Less than 50% in macroadenoma
- Recurrence
  - 3-10% in patients with initial success
  - 19% in patients with lower initial surgical cure

Dopamine Agonists – Cabergoline

- Inhibits GH secretion
- Normal IGF-1 in 34%
- When added to somatostatin analog 52% normal IGF-1
- Reduce tumor size - occasionally

Cabergoline 0.5 mg per week to 1 mg twice per week

- Side effects
  - Nausea
  - Lightheadedness
  - Mental fogginess
  - High doses – valvular heart disease, but not with smaller doses (less than 2 mg per week)

- GH receptor antagonist inhibits growth hormone action
- Pegvisomant daily SQ 10-30 mg per day
  - Higher doses in women with increase in weight and higher IGF-1
  - Normal IGF-1 in 56.6%
- Increase in GH
  - Adenoma size may grow
  - MRI yearly

Pegvisomant

Side effects

- Elevated LFT
- Lipohypertrophy at injection sites and distant sites
- Combination with somatostatin analogs not better

Radiation Therapy

- Decrease in size, GH and IGF-1 takes many years
  - X radiation from linear accelerator
  - Conventional radiation
  - IMRT (intensity modulated radiation therapy) CyberKnife
- Gamma radiation – Gamma Knife from cobalt source
- Proton from cyclotron

Clinical Case 1

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- History
- Exam
- Endocrine causes
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Labs

- Glucose 170
- A1c 8.7
- GH 15, 28.4
- IGF1 (normal 41-279)
  - 334
  - 482
- MRI
  - 1 cm pituitary mass

One year postop

- On metformin
- A1c 5.8
- IGF1 98 (normal 41-279)

Clinical Case 2

57-year-old female with multiple sclerosis,
hypertension and multinodular goiter with
subclinical hyperthyroidism, treated with
methimazole. The patient had increased
sweating and soft tissue swelling.

Clinical Case 2

The patient has clinical features of Acromegaly.

- Lab tests
- MRI of pituitary
- MRI and refer to neurosurgeon

- IGF1 489, 30 ng/mL
- OGTT with GH 2.6, 2.0, 3.0, 2.5, 2.8 ng/mL
- MRI of pituitary – partial empty sella

- GHRH 6 pg/mL (normal 5-18)
- McCune-Albright Syndrome?
- GNAS 1 gene mutation negative

55-year-old obese male with erectile dysfunction. He was told he had low testosterone and was treated with testosterone. He had no improvement, but had headaches, weakness, and vision problems. He wants an increase in the
dose of testosterone.

- Continue same dose or increase
- ?

Factors Affecting Prolactin

- Physiologic
  - Pregnancy
  - Nursing
  - Nipple stimulation
  - Stress
  - Sleep
  - Exercise

Pharmacologic Factors

- TRH
- Estrogen
- Dopamine antagonists
- Phenothiazines
- Haloperidol
- Risperidone
- Metoclopramide
- Reserpine
- Methyldopa
- Cimetidine
- Verapamil

Pathologic

- Pituitary tumor
- Hypothalamic/pituitary stalk lesions
- Chest wall lesions
- Hypothyroidism
- Chronic renal failure
- Severe liver disease

Hyperprolactinemia

- Premenopausal : Infertility, amenorrhea or oligomenorrhea, galactorrhea, mineral lower spine and forearm bone mineral density
- Postmenopausal : Headaches, impair vision or incidental finding with MRI
- Men: Decreased libido, impotence, infertility

Diagnosis

- Serum prolactin 5-20 ng/mL
- Macroadenoma – Hook effect causes low values
- Repeat assay using a 1:100 dilution
- Macroprolactin
  - Prolactin bound to immunoglobulin G (IgG)
  - Not significant directly, but can be misdiagnosed as hyperprolactinemia

Evaluation

- History
  - Pregnancy, medications, thyroid, renal failure
- Exam
  - VF, chest wall injury, hypothyroidism, hypogonadism
- Lab
  - Thyroid, prolactin, other pituitary? hormones

Adenoma Size

Microadenoma

< 1 cm, prolactin < 200 ng/mL

1-2 cm 200-1000 ng/mL

> 2 cm 1000 – 50,000 ng/mL

none – adenomas rarely > 200 ng/mL

Indications For Treatment

- Neurologic symptoms due to
  tumor size
- Hypogonadism, galactorrhea
- Trying to conceive

Hyperprolactinemia

Treatment

- Dopamine agonists
  - Decrease prolactin and size of tumor
- Cabergoline
  - 1-2/week
  - High dose in Parkinson's
  - Valvular heart disease
  - Bromocriptiris bid
- Pergolide
  - Valvular heart disease with high doses
- Quinagolide
  - Not available

Adverse Effects

- Nausea, postural hypotension mental fogginess, start small dose
- Valvular heart disease seen with high dose in Parkinson's disease
- Low dose – not associated

Efficacy

- In more than 90%, greater decrease in prolactin, the greater decrease in tumor size
- Effect blunted by use of medications known to raise serum prolactin
- Time course: follow up in 2-3 weeks

44-year-old male with history of erectile dysfunction. Seen at men's clinic and told he had low testosterone. He was treated with testosterone injections but no improvement. He later tried pellet implants. The patient was seen at the office requesting high dose of testosterone.

- Increase dose
- Try testosterone cream
- See psychologist for ED
- ?

44-year-old male with allergies, headaches, obesity and erectile dysfunction.

- Further history
- CT of head and sinuses
- Lab tests

CT large pituitary tumor in 1994.
Prolactin 490.
Many surgeries.
Radiation therapy – multiple.
Chemo – multiple.
Histology – rapidly growing, aggressive
tumor.
In 2017 – prolactin of 580.
Hypopituitarism.
In 2017 – pituitary mass 5 cm with suprasellar extension

Clinical Cases – Pituitary

30-year-old female with history of hyper- prolactinemia and pituitary microadenoma in the past (prolactin = 40).

Seen in follow-up and recent prolactin was 50 ng/mL

- History
- Labs
- Repeat MRI

70-year-old female admitted with syncope. CT of the head revealed pituitary tumor. Seen by neurosurgeon in hospital and sent home. Free T4 was low and house staff called in a prescription for L-Thyroxine. Seen two days later at the ER with extreme weakness,
dizziness and low blood pressure.

Chronic Primary Adrenal Insufficiency

- Symptoms of glucocorticoid, mineralocorticoid and, in women androgen deficiency
- Onset insidious
- Fatigue
- Weight loss
- Nausea
- Vomiting
- Abdominal pain
- Muscle and joint pain
- Postural hypotension
- Salt craving

Adrenal Crisis

- Shock, anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, confusion, coma
- Both glucocorticoid and mineralocorticoid involved

- Hemorrhage or infarction
  - Shock
  - Abdominal or flank pain
  - Nausea
  - Confusion
  - Fever
  - Not pigmented
  - Abdominal rigidity
  - Lower hemoglobin
  - High potassium

- Risk Factors
  - Anticoagulation
  - Coagulopathy
  - Meningococcemia – petechiae – Waterhouse-Friderichsen Syndrome
  - Other infections

- Secondary or Tertiary Adrenal Insufficiency
  - Other anterior pituitary hormone deficiency symptoms
  - Hypoglycemia
  - Hypotension
  - Shock
  - Usually normal mineralocorticoid function

- Signs
  - Hypotension
  - Hyperpigmentation
  - Due to increased proopiomelanocortin (POMC)
  - Cleaved into ACTH and MSH
  - Auricular cartilage calcification in men
  - Vitiligo
  - Splenomegaly
  - Lymphoid tissue hyperplasia – tonsils
  - Polyglandular autoimmune syndrome

- Lab – hyponatremia in 70-80% due to mineralocorticoid deficiency and cortisol deficiency causing increased ADH
- Elevated potassium in 40%
- High calcium rarely seen with acute
  renal insufficiency
- Hypoglycemia
- Normocytic anemia

Secondary or Tertiary Adrenal Insufficiency

- Fatigue
- Muscle and joint pain
- Psychiatric symptoms
- Hyperpigmentation not present
- Dehydration not present
- Low sodium due to SIADH or cortisol deficiency
- High potassium not present
- Hypoglycemia more common
- Deficiency of other pituitary hormones
- Headache
- Visual field defects

Causes of Primary Adrenal Insufficiency

- Autoimmune adrenalitis
- Antibodies in 86%
- First evidence
  - Elevated plasma renin activity with normal or low aldosterone
  - Zona glomerulosa involved
  - Later zona fasciculata dysfunction
  - Cortisol deficiency
  - Elevated ACTH
  - Other endocrine disorders 50-60%

Polyglandular Autoimmune Syndrome

- Type 1 (rare)
  - Hypoparathyroidism first
  - Chronic mucocutaneous
  - Candidiasis in mouth, nail beds
  - Adrenal insufficiency – later
  - Primary hypogonadism in 60%
  - Malabsorption in 25%

Polyglandular Autoimmune Syndrome

- Type 2
  - More prevalent than Type 1
  - Adrenal insufficiency – main feature
  - Autoimmune thyroid disease (Schmidt's syndrome)
  - Type 1 diabetes also common
  - Familial – more in women
  - Primary hypogonadism
  - Hyperparathyroidism not present
  - Hypopituitarism
  - Other - vitiligo, myasthenia gravis, RA

Infectious Adrenalitis

- TB – enlarged gland – later normal or small
- Disseminated fungal infections
- HIV less with treatment

Adrenal Hemorrhagic Infarction

- Acute adrenal crisis
- Result of bilateral adrenal infarction caused by hemorrhage or adrenal vein thrombosis
- Risk Factors
  - Anticoagulant drug or heparin therany
  - Thromboembolic disease
    - Hypercoagulable states
      - Trauma
      - Sepsis
      - Infection – Meningococcy, Ecoli
- CT for diagnosis

Metastatic Disease

- Lung
- Breast
- Melanoma
- Stomach
- Colon
- Low incidence of clinical adrenal insufficiency

Drugs

- Inhibit cortisol synthesis
  - Etomidate (anesthetic – sedative)
  - Ketoconazole (antimycotic)
  - Fluconazole
  - Metyrapone
  - Suramin (antiparasitic in prostate cancer)
- Accelerate metabolism of cortisol
  - Phenytoin, barbiturates, rifampin
  - Mitotane treats adrenal tumors

- Suppressed CRH or ACTH
  - Glucocorticoid
  - Megestrol
  - Opioids
- Potentiate glucocorticoid effects
  by decreasing its metabolism
  (Example: ritonavir)

Treatment of Adrenal Crisis

- Collect blood for cortisol, ACTH, aldosterone, renin, CMP in two tubes
- ACTH stimulation test ? later
- One to three liters of 5% dextrose and 0.9% saline 12-24 hours IV
- No hypertonic saline
- Dexamethasone 4 mg IV (in non-diagnosed)
- Hydrocortisone 100 mg IV preferred if potassium is high
- Continue hydrocortisone 50 mg IV q. 8 h.

Chronic Adrenal Insufficiencies

Short-acting:

- Hydrocortisone, 2 or 3 doses, total 15-25 mg
- Normal subjects secrete little cortisol 6 p.m. to 3 a.m.
- Has mineralocorticoid activity
- Fludrocortisone decreased (0.1 mg – 0.05 mg per day)

Long-acting:

- Dexamethasone 0.25 mg – 0.75 mg daily
- Prednisone 2.5 mg – 7.5 mg daily

Monitoring dose of steroids

- Lowest dose
- Avoid signs and symptoms of glucocorticoid deficiency or excess

Plasma ACTH

- On mineralocorticoids
- BP low or high
- Potassium

Plasma renin upper normal range

- Adjust only if symptomatic or abnormal labs

Androgen replacement (DHEA) in women

- Mood or quality of life better ?
- DHEA 25-50 mg daily
- Side effects
  - Hirsutism, acne
  - ? long-term effects
- Other hormones - thyroid

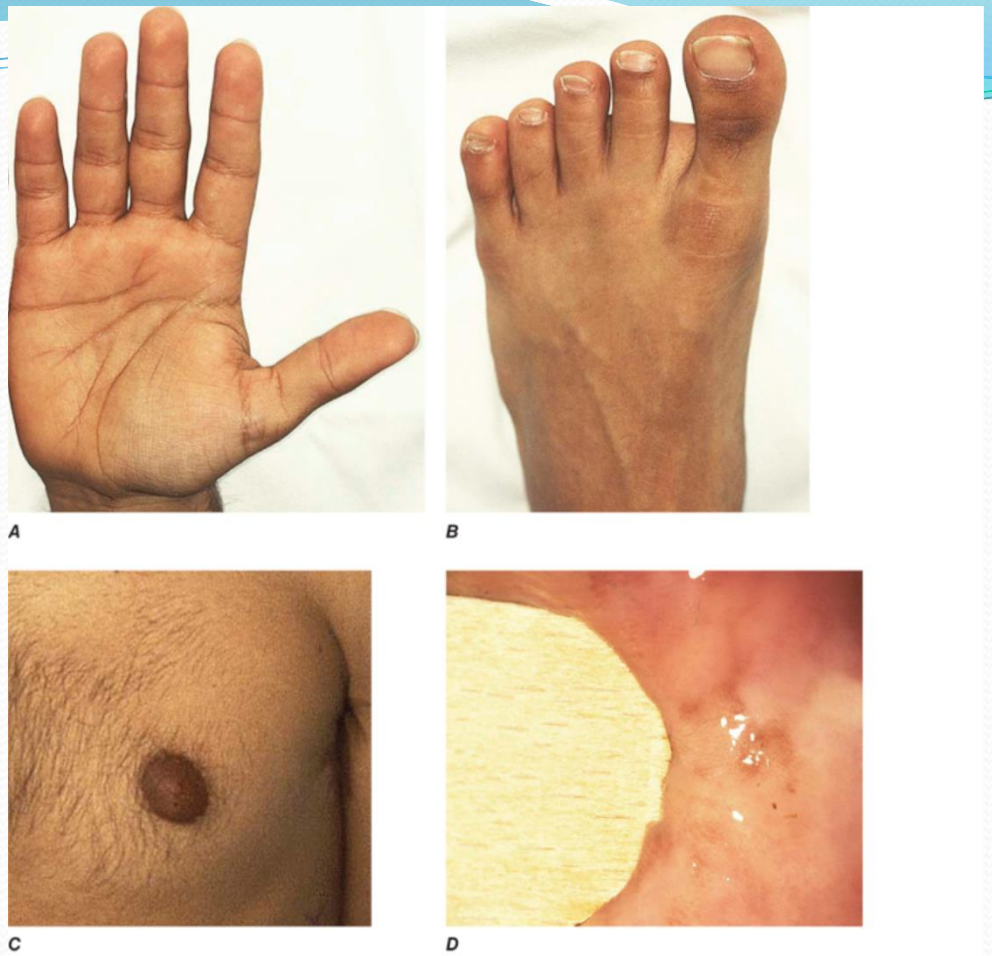
Illness or Surgery

- Minor illness patient 3 x 3
  - If nausea or vomiting inject
- Surgery
  - Minor – hydrocortisone 25 mg first day, second day usual dose
- Moderate surgery (gallbladder, joint)
  - Divided IV 50-75 mg first and second day, third day usual dose
- Major surgery
  - IV 100-150 mg for two or three days
  - Start preop

Patient Instructions

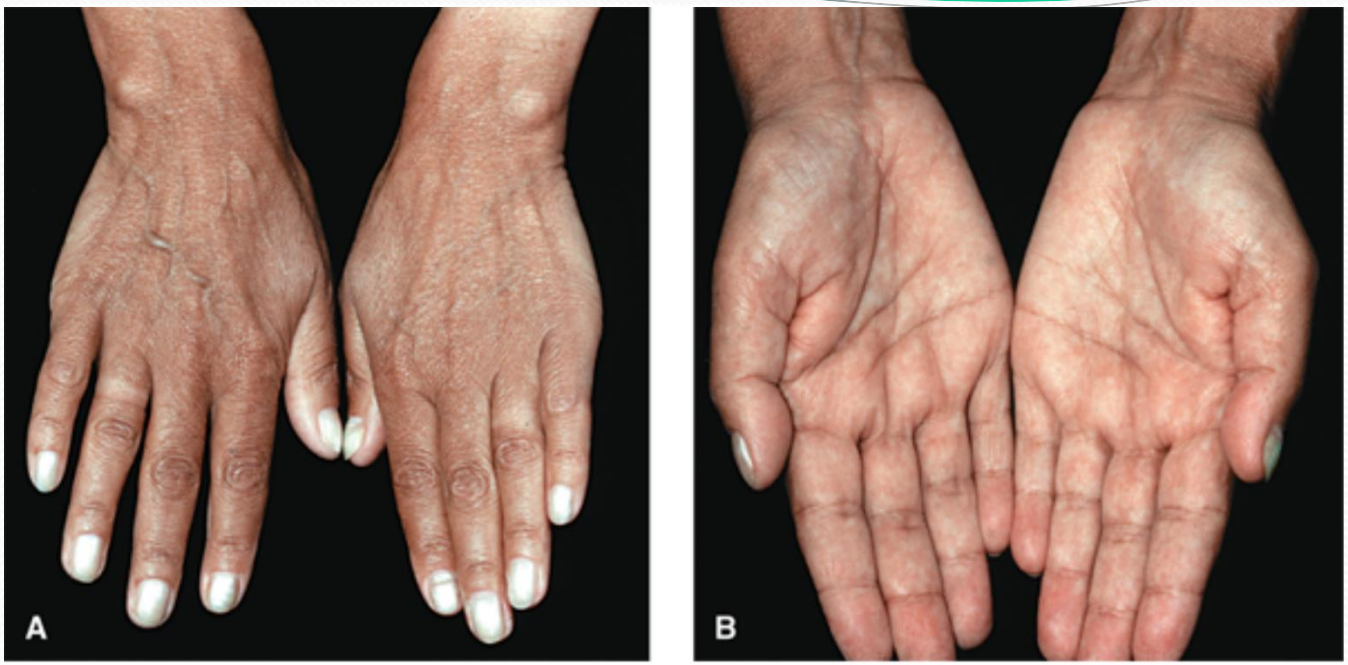
- Medic Alert bracelet with info
- Always carry oral steroids
- Injectable hydrocortisone 100 mg
- 0.9% saline and syringes
- Instructed to inject IM or SQ
- Low threshold to injection
- 3 * 3 Rule

42-year-female OR nurse with fatigue,
Anorexia and weight loss. Friends Noted pale skin. Seen by a psychiatrist
for depression. Had low blood pressure.



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

Clinical features of Addison's disease. Note the hyperpigmentation in areas of increased friction including (A) palmar creases, (B) dorsal foot, (C) nipples and axillary region, and (D) patchy hyperpigmentation of the oral mucosa.



Addison disease (A) Hyperpigmentation representing an accentuation of normal pigmentation of the hand of a patient with Addison disease. (B) Note accentuated pigmentation in the palmar creases.

Source: Endocrine, Metabolic and Nutritional Diseases, *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 7e*

Citation: Wolff K, Johnson R, Saavedra AP. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 7e*; 2013 Available at: http://accessmedicine.mhmedical.com/content.aspx?bookid=1700&sectionid=113785382&jumpsectionID=113785442 Accessed: March 17, 2017

40 year old female with fatigue, weight loss, and darkening of lips attributed to biting on a pen and pencil – seen by a psychiatrist

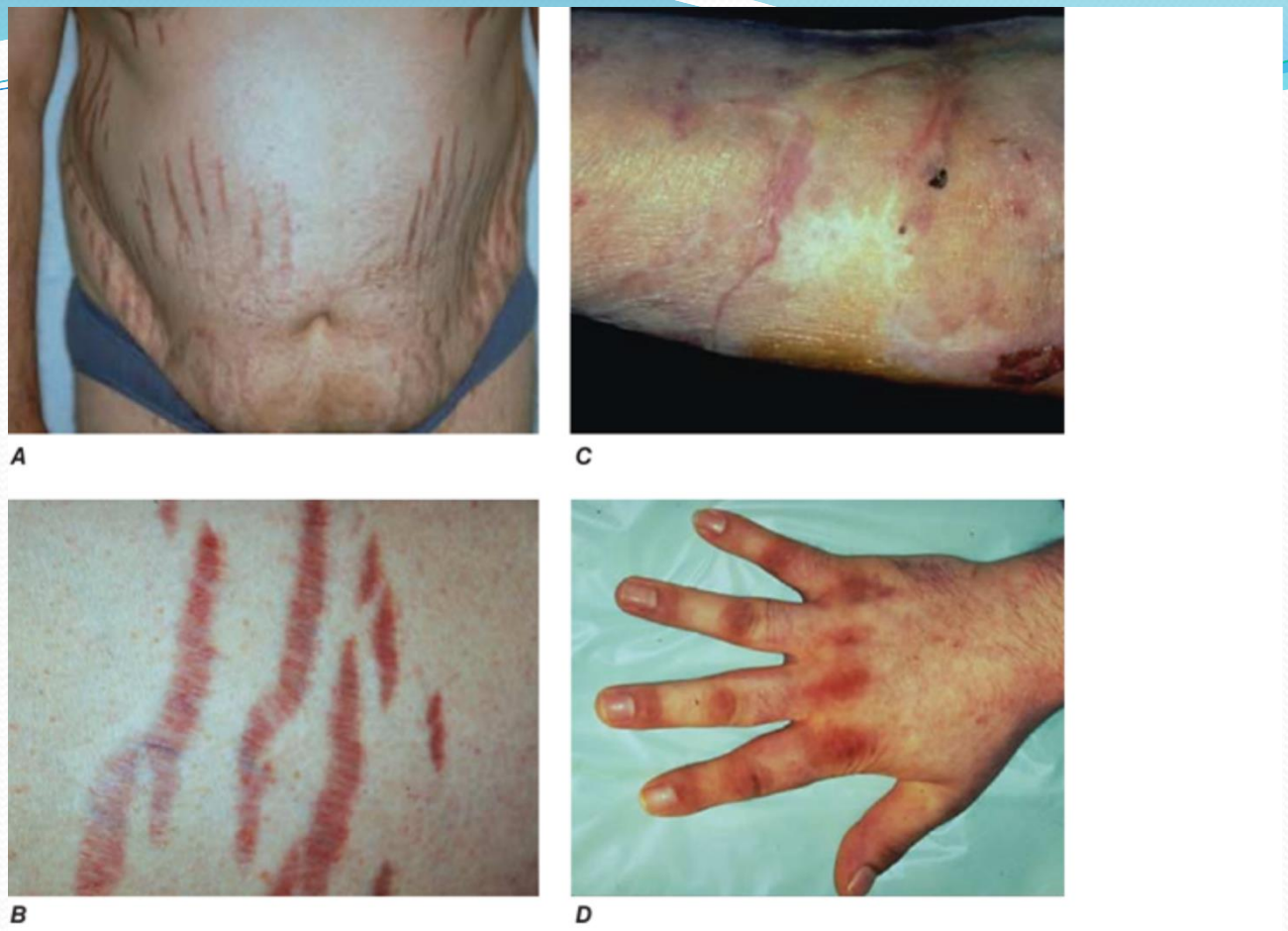
- History
- Exam
- Lab Test

32-year-old female with fatigue, dry skin,
amenorrhea and weight loss. History of low blood pressure and past history of pulmonary sarcoidosis.

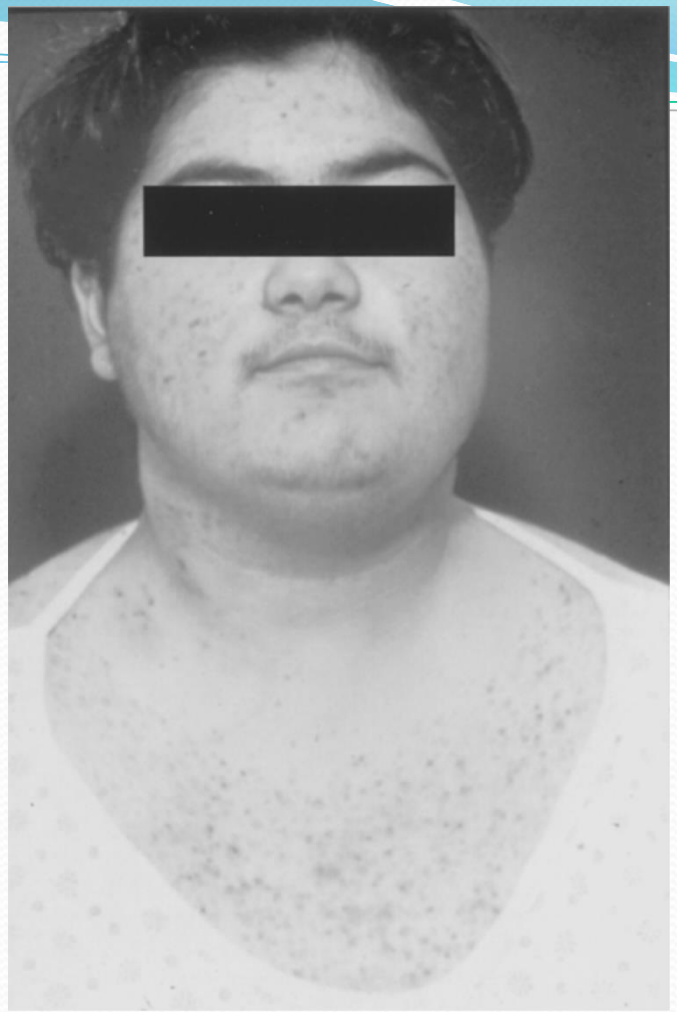
- History
- Lab
- MRI
- Pulmonary evaluation

Cushing's Syndrome

- Who should be tested:
  - Clinical features
  - Obesity 90%
  - Hypertension 85%
  - Skin – striae 50%
  - Facial plethora 70%
  - Hirsutism 75%
  - Musculoskeletal
    - Osteopenia 80%
    - Weakness 65%



Clinical features of Cushing's syndrome. A. Note central obesity and broad, purple stretch marks (B. close-up). C. Note thin and brittle skin in an elderly patient with Cushing's syndrome. D. Hyperpigmentation of the knuckles in a patient with ectopic adrenocorticotropic hormone (ACTH) excess.



Some characteristic features of Cushing’s syndrome—moon facies, hirsutism, and acne.

- Neuropsychiatric
  - Depression, emotional lability
- Gonadal dysfunction / Menstrual disorder 70%
- Impotence 85%
- Metabolic
  - Glucose intolerance 75%
  - Hyperlipidemia 70%

- Unusual Findings For Their Age
  - Hypertension, osteoporosis in young
  - Multiple features of Cushing's Syndrome such as facial plethora, proximal myopathy, striae

- Who should be tested
  - Unexplained features at any age
  - Resistant hypertension
  - Osteoporosis
  - Adrenal incidentaloma

- Exclude exogenous glucocorticoids
  - Steroid therapy
    - Oral, injected, topical, inhaled
  - High dose megestrol (progestins) has intrinsic glucocorticoid activity

- Clearance of steroid delayed by ritonavir
- Herbal creams with glucocorticoids
- Factitious Cushing's Syndrome
  - Low or erratic cortisol studies
  - Detect synthetic gludocorticoids in urine

Initial Testing for Cushing's Syndrome

- 24-hour urine free cortisol x 2
- Late night salivary cortisol x 2
- Overnight 1 mg dexamethasone suppression test < 1.8 mcg/dL

- Exclude physiologic hypercortisolism
  - Pseudo CS
  - Seldom have cutaneous or muscle signs
  - Pregnancy
  - Severe obesity
  - PCOS
  - Depressive disorders
  - Poorly controlled diabetes
  - Chronic alcoholism

- Physiologic Hypercortisolism
  - Unlikely to have clinical features of Cushing's Syndrome
  - Physical Status – illness, surgery malnutrition, anorexia nervosa, intense chronic exercise
  - Hypothalamic amenorrhea
  - High CBG (corticosteroid binding globulin)
  - Has increased serum cortisol not UFC
  - Glucocorticoid resistance

- Cushing's Syndrome Confirmed
  - Two different tests are abnormal
  - Physiologic hypercortisolism excluded
  - UFC three times upper limit of normal
  - Late night salivary cortisol > 1.6 mg/mL
  - Late night serum cortisol > 7.5 mcg/dL

- Cushing's Syndrome Confirmed
  - Dexamethasone suppression test:
    - Two-day 1 mg dexamethasone at 11 p.m. to 12 a.m.
    - Serum cortisol at 8 a.m. the next morning less than 1.8 mcg/dL
  - Two-day, 2 mg test:
    - Dexamethasone 0.5 mg every 6 hours for eight doses
    - Measure serum cortisol after 2 or 6 hours (<1.8 mcg/dL

Establish the Cause of Cushing's Syndrome

- Primary adrenal disease versus ACTH secreting tumor
- Measure plasma ACTH
  - Normal: 8 a.m. 20-80 pg/mL

    4 p.m. < 10 pg/mL

    1 hour into sleep < 5 pg/mL

- ACTH dependent from pituitary
  or
  non-pituitary source
  - ACTH > 20 pg/mL

- ACTH independent – adrenal source
  - ACTH < 5 pg/mL

ACTH Independent Cushing's Syndrome

- Primary adrenal disease
  - ACTH < 5 pg/mL
  - Cushing's Syndrome of adrenal gland
- Adrenal adenoma (10%)
- Adrenal carcinoma 8%
- Micronodular hyperplasia < 1%
- Macronodular hyperplasia <1%

ACTH Dependent Cushing's Syndrome

- ACTH >20 pg/mL
- Cushing's disease 68%
- Ectopic ACTH syndrome 12%
- Ectopic CRH syndrome <1%

- High dose dexamethasone suppression test
  - 8 mg dexamethasone at 11 p.m. - midnight
  - Cortisol at 8 a.m. the next morning
  - < 5 mcg/dL in Cushing’s disease

CRH Stimulation Test

- Cushing's disease – increased ACTH and cortisol
- Adrenal tumor – does not respond
- Ectopic ACTH – does not respond
- Vasopressin or DDAVP also stimulates

  release in Cushing's disease

Inferior Petrosal Sinus Sampling (IPSS)

- The most direct way to distinguish pituitary from non-pituitary ACTH dependent Cushing's syndrome:
  - Use bilateral simultaneous IPSS with CRH
  - Central to peripheral plasma ACTH gradient
    - > 20 before CRH
    - > 30 after CRH

Imaging Studies

- MRI
  - Unenhanced
  - Gadolinium enhanced
- Ectopic ACTH
  - CT of chest
  - MRI, PET, Octreotide scan

58-year-old female with diabetes,
proximal muscle weakness, hyper-
tension, and central obesity.

- History
- Labs
- CT of abdomen

61 year old female with Cushing syndrome

- Cortisol pm 46.4 µg/dl (2 – 17)
  Low dose DST cortisol 29.2 µg/dl
- High Dose DST 35.5 µg/dl
- ACTH : 119 – 187 pg/dl (9 -52)
- 24 hour urine free cortisol 55 – 540 µg/24 hrs (3 – 51)

2 day DST – cortisol 70.7 µg/dl
ACTH 93 pg/dl

		After CRH
• IPSS central to peripheral ratio	65 (> 2)	230 (> 3)
• Right to left ratio	21	86

- MRI Normal Sella

Trans nasal transphenoidal surgery

- Total hypophyrectomy

but cortisol elevated 17 – 33.6 **µg/dl**

- MI 16th day post op
- Autopsy : intracavernous ectopic ACTH
  - Secreting microadenoma

45-year-old female with past history of anorexia. Treated with megestrol until two
weeks ago. Admitted with extreme weak-ness and nausea for one week. On exam
she appeared cushingoid, but lab tests revealed a low cortisol of 3.

- History
- DST
- Salivary cortisol at 11 p.m.
- CT
- Treat

Clinical Cases - Adrenal

65-year-old male with abdominal pain. CT of the abdomen revealed a 6.5 cm left adrenal mass.

- History
- Labs
- Biopsy of adrenal
- Surgery

Adrenal Incidentaloma

- Mass lesion > 1 cm with CT or MRI
- Prevalence on abdominal CT
  - 4.4%
  - older subjects 10%
- Is it malignant?
- Is it functioning?

Bilateral Adrenal Masses

- Test for hypo- or hyperfunction
- 10-15% of adrenal incidentaloma
- Seen in: metastatic disease, adrenal hyperplasia, cortical adenomas, lymphomas, infections (TB, fungal), hemorrhage, ACTH dependent Cushing's disease, pheochromocytoma, primary aldosteronism, amyloidosis, bilateral macronodular adrenal hyperplasia (BMAH)

Evaluation For Malignancy

- 2-5% adrenal cancer
- 0.7-2.5% nonadrenal metastasis
- Benign adenomas
  - Round
  - Homogeneous density
  - Smooth contours and sharp margins
  - < 4 cm
- Low CT – a Henuation value < 10 Hu
- Rapid Contrast medium washout > 50% at 10 mins.

Adrenal incidentaloma fine needle aspiration: Cannot distinguish benign mass from adrenal carcinoma, but distinguish benign adrenal tumor and metastatic tumor warning

Hormonal Secretion

- Benign, nonfunctioning, 89.7%
- Subclinical CS 6.4%
- Pheo 3.1%
- Primary aldosteronism 0.6%
- Test for subclinical CS and Pheo
- Hypertensive – primary aldosteronism

Subclinical CS

Glucocorticoid secretory autonomy without clinical manifestations of CS, but may have hypertension, diabetes, and vertebral fractures

Diagnosis

- 1 mg dexamethasone suppression test (DST)
- If abnormal, 24-hour urine free cortisol
- ACTH undetectable
- High dose 8 mg dexamethasone, cortisol > 5 mcg/dL
- DHEA sulfate if undetected suggests chronic suppression of ACTH

- Pheo 3%
- Plasma fractionated metanephrines
- 24-hour urine for fractionated metanephrines and catecholamines
- Aldosteronomas < 1% ifhyper-tensive, plasma renin activity and plasma aldosterone

Clinical Cases - Adrenal

65-year-old male with abdominal pain. CT of the abdomen revealed a 6.5 cm left adrenal mass.

- History
- Labs
- Biopsy of adrenal
- Surgery

53-year-old female with abdominal pain,
nausea and vomiting. CT of the abdomen
revealed a 3.5 cm right adrenal mass.

- History
- Labs
- Biopsy of adrenal

55 year old female admitted to hospital for abdominal hernia repair. History of adrenal nodule but lab test not available.

- Surgeon wants medical clearance
  - History
  - Routine lab
  - Ok for surgery

Clinical Cases

IGF-1

- Reflected integrated GH secretion during the preceding day or longer
- Does not vary with exercise, food or sleep
- IGF-1 highest in puberty and declines gradually
- Normal in a 70 year old may be elevated

OGTT With GH

- Useful after surgical treatment
- Not with medical therapy
- Standard assay > 1 ng/mL
- Newer immunoradiometric immunochemiluminescent > 0-3 ng/mL

Determining Sources of Excess GH

- Pituitary MRI
  - 75% macroadenoma 10 mm or more
  - Rarely empty sella
  - 10-20% normal in subjects have MRI or autopsy evidence of pituitary microadenoma

Rare Causes

- Pituitary somatotroph cancer
- Hypothalamic tumor secreting GHRH
- Non-endocrine tumor secreting GHRH
- Ectopic secretion of growth hormone

- Stereotactic radiosurgery
- Radiation administered as a single dose with
  - Linear accelerator
  - Gamma radiation
  - Protons
- Convenient
  - Protons
  - Faster hormone change
- Adenoma must be separate from optic chiasma and optic nerve

Medical Therapy

- Predictors of Response
  - Smaller, more active, densely granulated respond well
  - Sparsely granulated, large, more invasive less responsive
  - MRI hypointense T2 signal better response

Due to Excessive Secretion of Growth Hormone

- Commonly due to GH secreting adenoma of the anterior pituitary
- Activating mutation of the alpha subunit of the guanine nucleotide stimulatory protein (Gs-alpha) gene in 40%
- Pituitary tumor transforming gene

Rare Causes

- GHRH by hypothalamic tumors and ectopic GHRH by neuroendocrine tumors – carcinoid and small cell lung cancer

- Ectopic GH ? By neuroendocrine tumors

- Clinical features due to high serum GH and IGF-1
- Somatic effect
  - Stimulates growth of many tissues
- Metabolic effect
  - Nitrogen retention
  - Insulin antagonism
- Due to its size
  - Headaches
  - Visual
- Insidious onset
  - 75% have macroadenoma

Excess growth hormone results in overgrowth of connective tissue, cartilage, bone, skin and visceral organs

Other complications

- Cardiovascular disease
- Sleep apnea
- Metabolic disorders
- Colon neoplasia

ACROMEGALY

- Hypersecretion of growth hormone
- Hepatic secretion of insulin-like growth factor (IGF-1)
- Clinical features of acromegaly

- Diagnosis often delayed
- Slow progression
- Considered rare 30-70/million
- Recent data suggest 1000/million
- Type 2 diabetes 450/million

CLINICAL FEATURES

- Macrognathia (enlarged jaw)
- Facial features – coarse, enlarged nose, frontal bones and jaw, upper incisors spread apart
- Enlarged hands, enlarged feet, glove size, ring size, increased shoe size

OTHER FEATURES

- Cardiovascular disease
- Sleep apnea
- Type 2 diabetes
- Arthropathies
- Carpal tunnel syndrome
- Pituitary tumor size (headache, visual field defects)

DIAGNOSTIC EVALUATION

- Biochemical test
- Radiological – pituitary MRI
- Cause > 95% somatotrophy adenoma of the pituitary

BIOCHEMICAL TESTS

- Serum IGF-1 – does not vary with food, exercise or sleep, or hour to hour like GH
- Reflect integrated GH secretion during the preceding day or longer

IGF-1

- Levels highest during puberty
- Levels lower in adult over 60 years
- Lower in hypothyroidism

Low Serum IGF-1 In

- Hypothyroidism
- Malnutrition
- Poorly controlled diabetes type 1
- Liver failure
- Oral estrogen use

Lab

- Difference in calibration
- Standards for the assay

75 gm OGTT With GH

- Most specific
- GH falls to less than 1 ng in 2 hours (with radioimmunoassay)
- With newer immunoradiometric
- Immunochemiluminescent
- GH falls to less than 0.3 ng/mL
- Best test after surgery
- Not with medical therapy

GH

- Random test not useful
- Pulsatile, diurnal
- Fasting, sleep, exercise, stress
- Clearance rapid plasma half life 20 minutes
- High in liver disease, malnutrition, uncontrolled diabetes

Other Tests

- TRH test (500 mcg) IV
- GH rises by 50% at 20-30 minutes
- L-Dopa (500 mg) p.o.
  - Reduces GH by 50%
  - Raises GH in normal
- Serum IGF BP – 3
  - GH dependent
  - Elevated in acromegaly but not always

Determining Source of Excess GH

- Pituitary MRI
- 75% macroadenoma (10 mm or more)
- Rarely empty sella
- 10-20% normal ____ MRI
- Autopsy evidence of pituitary microadenoma

Rare Causes

- Pituitary somatotrophic cancer
- Hypothalamic tumor secreting GHRH
- Non-endocrine tumor secreting GHRH
- Ectopic secretion of GH
- Test abdominal and chest imaging
- Catheterization studies

Ectopic GHRH

- Accounts for 0.5% of cases
- Measure serum GHRH

Presentation Based on Etiology

- Autoimmune
  - Shock
  - Abdominal pain
  - Hyperpigmented
  - Weight loss
  - Electrolyte abnormalities

Acromegaly – Goals of Therapy

- Lower IGF-1 to reference range for age and gender
- Serum growth hormone < 1 ng/mL after glucose load
- IGF-1 is a better test than growth hormone
- Normal growth hormone secretion not often achieved

Adrenal Incidentaloma

- CT scan
  - Lipid rich adrenal cortical adenoma (CT of image blackish, less dense is attributed to radiograph attenuation)
  - Intracytoplasmic fat is in adenoma, low attenuation
  - Non-adenomas high attenuation measured in Hounsfield units

- Adrenal mass less than 10 HU on unenhanced CT that is density of fat (almost 100% benign)
- Adrenal cancer 36.9 +/- 4.1
- Metastasis 39.2 +/- 15.2
- Pheo 38.6 +/- 8.2
- Enhanced CT greater than 28 HU