PITUITARY ADENOMA

HORMONAL AND MEDICAL MANAGEMENT

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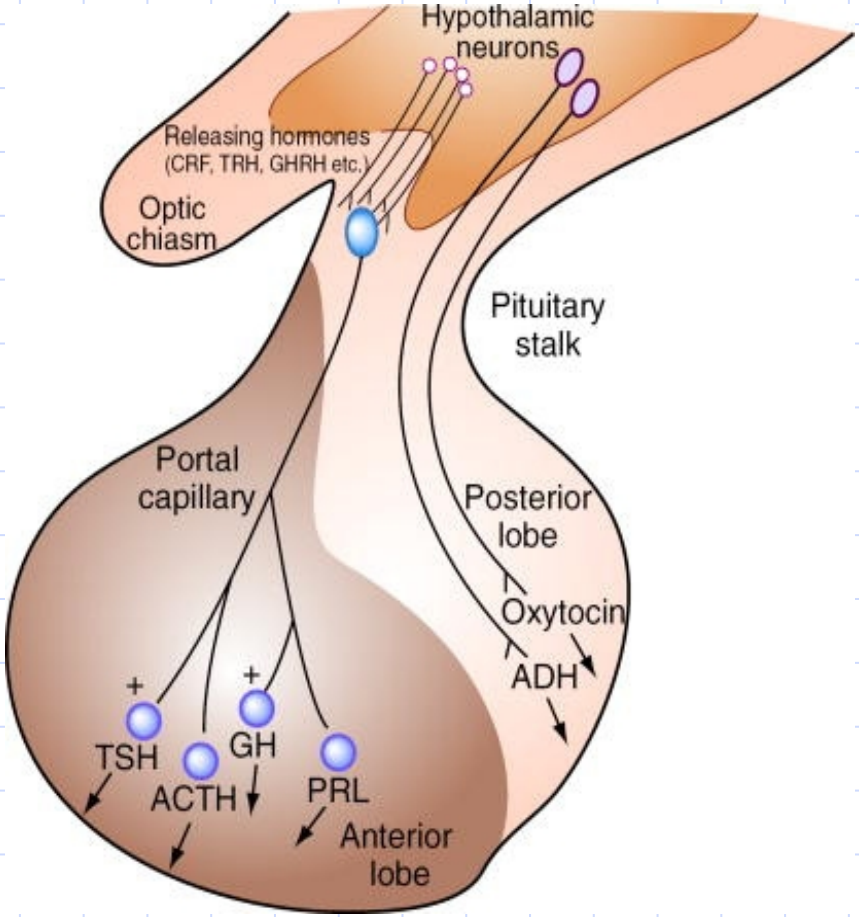

Hypothalamic neurons
Releasing hormones (CRF, TRH, GHRH etc.)
Optic chiasm
Pituitary stalk
Portal capillary
Posterior lobe
Oxytocin
ADH
+
+
TSH
GH
ACTH
PRL
Anterior lobe

CLASSIFICATION OF PITUITARY ADENOMAS ACCORDING TO ENDOCRINE FUNCTION

- Adenomas With
  - GH excess
  - PRL excess
  - ACTH excess
  - TSH excess
  - FSH / LH excess
  - PLEURI hormonal adenomas
- Adenomas With No Apparent Hormonal Function

Hormonal Evaluation

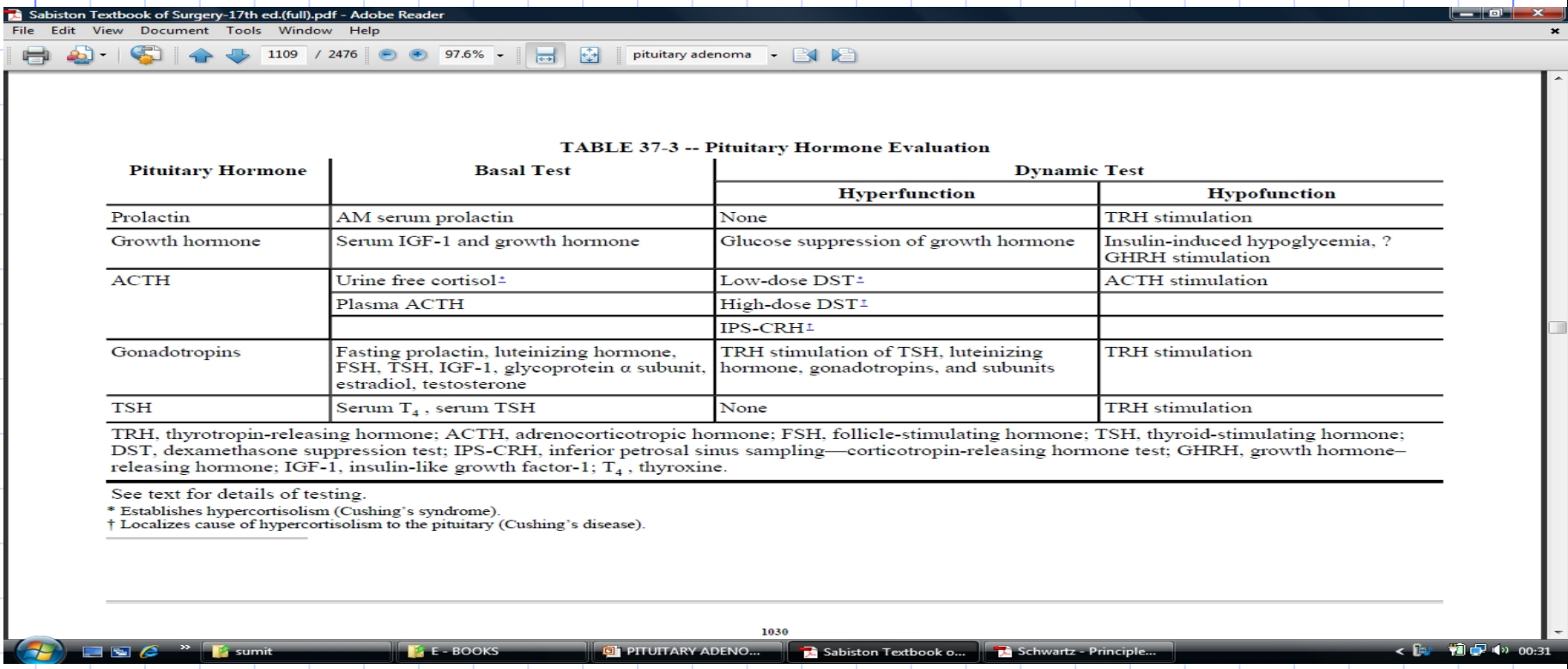


TABLE 37-3 -- Pituitary Hormone Evaluation

Pituitary Hormone	Basal Test	Dynamic Test	
		Hyperfunction	Hypofunction
Prolactin	AM serum prolactin	None	TRH stimulation
Growth hormone	Serum IGF-1 and growth hormone	Glucose suppression of growth hormone	Insulin-induced hypoglycemia, ? GHRH stimulation
ACTH	Urine free cortisol*	Low-dose DST*	ACTH stimulation
	Plasma ACTH	High-dose DST†	
		IPS-CRH†	
Gonadotropins	Fasting prolactin, luteinizing hormone, FSH, TSH, IGF-1, glycoprotein α subunit, estradiol, testosterone	TRH stimulation of TSH, luteinizing hormone, gonadotropins, and subunits	TRH stimulation
TSH	Serum T_4 , serum TSH	None	TRH stimulation

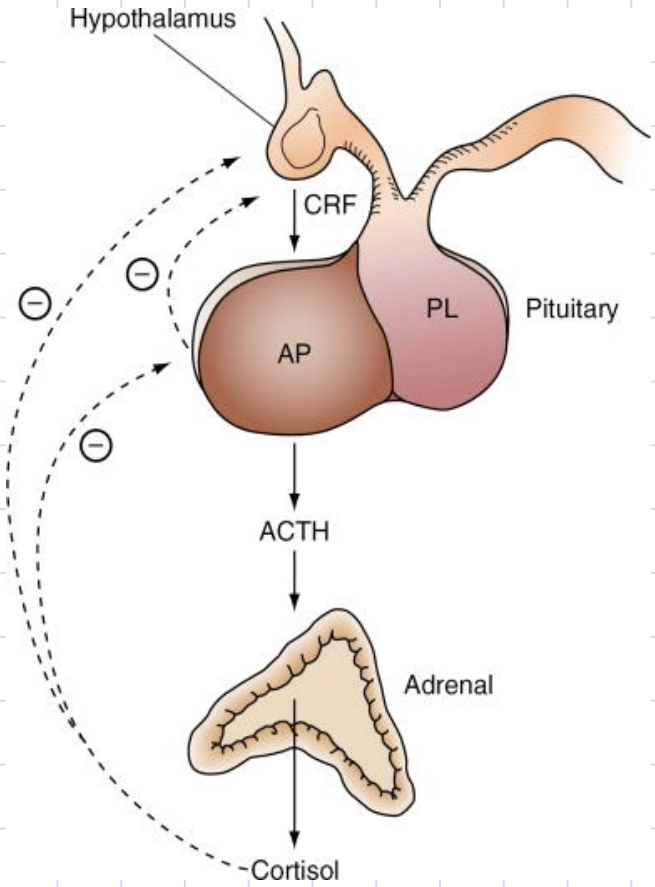
TRH, thyrotropin-releasing hormone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; DST, dexamethasone suppression test; IPS-CRH, inferior petrosal sinus sampling—corticotropin-releasing hormone test; GHRH, growth hormone–releasing hormone; IGF-1, insulin-like growth factor-1; T_4 , thyroxine.

See text for details of testing.

* Establishes hypercortisolism (Cushing's syndrome).

† Localizes cause of hypercortisolism to the pituitary (Cushing's disease).

HPA Axis:



Cushing's Syndrome vs. Cushing's Disease

- **Cushing's syndrome** is a syndrome due to excess cortisol from pituitary, adrenal or other sources (exogenous glucocorticoids, ectopic ACTH, etc.)

- **Cushing's disease** is hypercortisolism due to excess pituitary secretion of ACTH (about 70% of cases of endogenous Cushing's syndrome)

Evaluation Of Suspected Cushing`s Syndrome

- HISTORY: increased weight, growth retardation in children , weakness, easy bruising, stretch marks, poor wound healing, fractures, change in libido, impotence, irregular menses, mood changes
- EXAM –fat distribution, hypertension, proximal muscle weakness, thin skin and ecchymoses, purple striae, hirsuitism, acne, facial plethora, edema

Corticotroph adenomas

Laboratory Evaluation

- Establishing hypercortisolism
- Distinguishing ACTH- dependent from ACTH independent causes of hypercortisolism
- Differentiating Cushing's disease from ectopic states of ACTH excess

Establishing hypercortisolism

- Urinary free cortisol

  Sensitivity 45–71%,100% specificity

- Overnight dexamethasone suppression test or Low dose dexamethasone suppression test (Liddle test)

  (0.5mg qid 48 hrs)
  Cut off for serum cortisol < 1.8 mcg/dl (≤50 nmol/l).
  Sensitivity 95 % and specificity 88%
  Cushing's syndrome usually have levels >275 nmol/L (10 µg/dL)

- Nocturnal Salivary Cortisol

Nocturnal Salivary Cortisol:

- 93% sensitivity,100% specificity.
- levels < 4.0 nmol/l, the diagnosis of significant Cushing's syndrome is unlikely
- 7–8 nmol/l are abnormal

Establishing ACTH Dependency

Measurement of plasma ACTH levels

- ACTH level <1.1 pmol/L (5 pg/mL) by IRMA is consistent with an ACTH-independence
- Corticortroph adenoma :moderate elevation
- Ectopic ACTH producing lesion :marked elevation

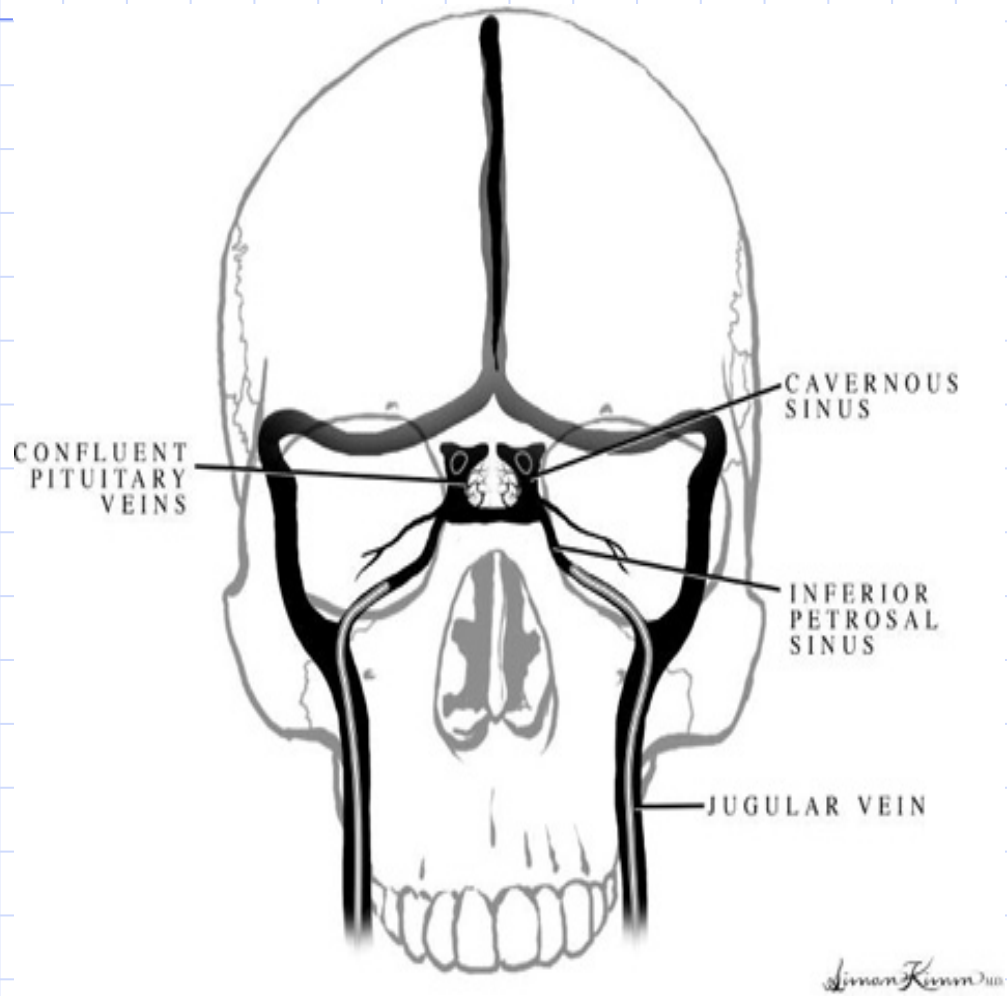
Differentiating Cushing's disease from ectopic states of ACTH excess

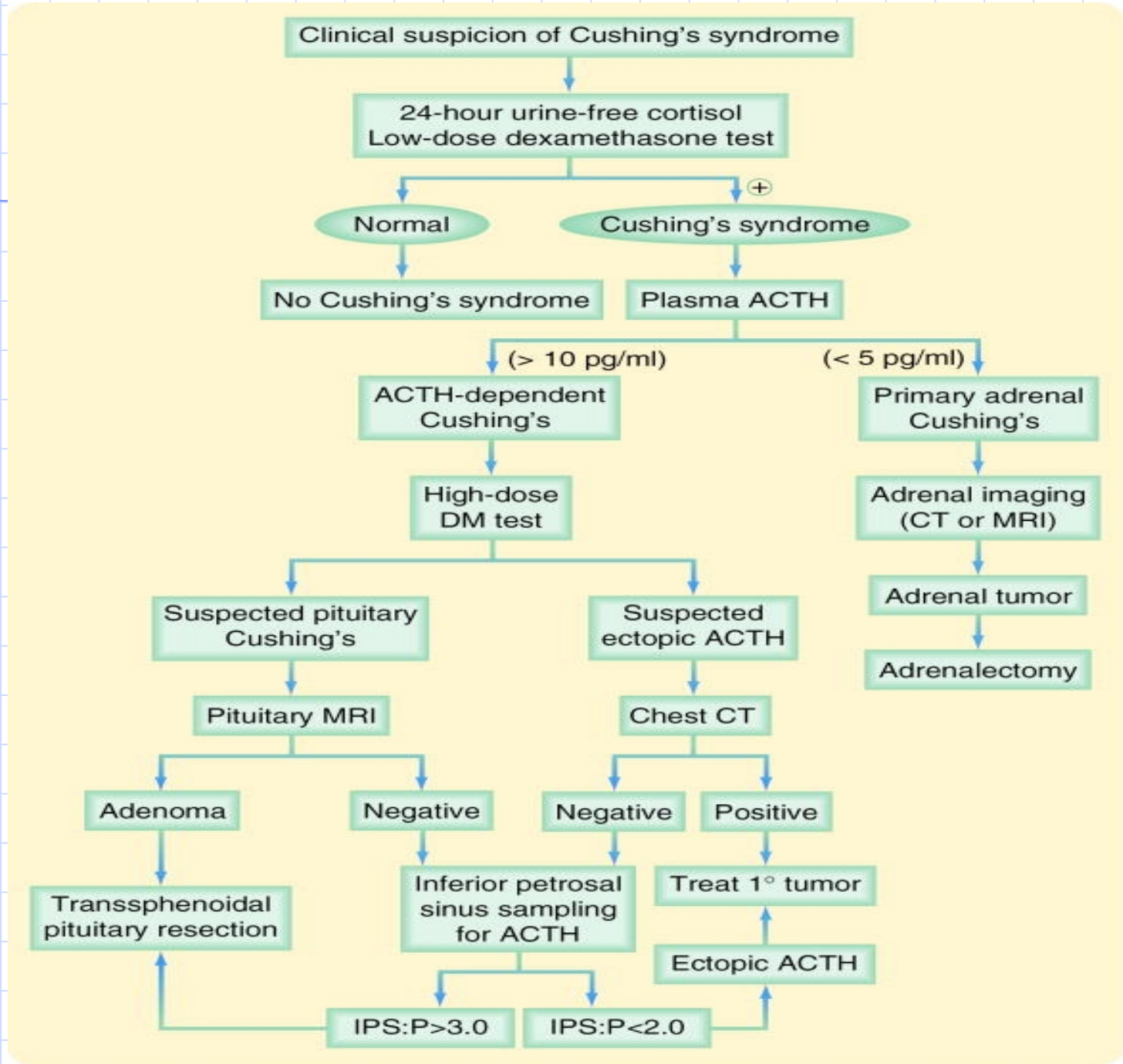
- High dose dexamethasone suppression test (2 mg qid for 48 hrs) and measurement of urinary cortisol/ 17- hydroxycoricosteroid
- Overnight 8 mg dexa morning serum cortisol
- CRH stimulation test.
- Metyrapone Test (inhibitor of 11β-hydroxylase)

Inferior petrosal sinus sampling

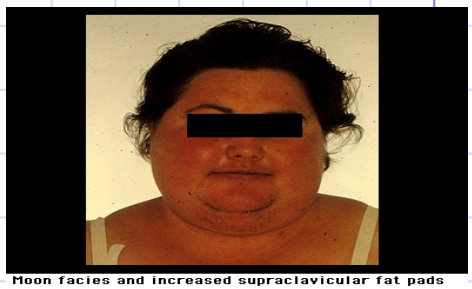
- Classical clinical and biochemical CD features with MRI negative patient equivocal suppression and stimulation test
- Diagnostic accuracy is 80-100%
- Blood samples are obtained at basal and 3,5,10 min after CRH administration and ips/ps ratio calculated
  ips/ps >3 CD
  ips/ps <2 ectopic
  rarely 2-3 ectopic
- IPS gradient helps in lateralization of adenoma

IPSS


CAVERNOUS SINUS
CONFLUENT PITUITARY VEINS
INFERIOR PETROSAL SINUS
JUGULAR VEIN


Clinical suspicion of Cushing's syndrome
24-hour urine-free cortisol
Low-dose dexamethasone test
+
Normal
Cushing's syndrome
No Cushing's syndrome
Plasma ACTH
(> 10 pg/ml)
(< 5 pg/ml)
ACTH-dependent Cushing's
Primary adrenal Cushing's
High-dose DM test
Adrenal imaging (CT or MRI)
Adrenal tumor
Adrenalectomy
Suspected pituitary Cushing's
Suspected ectopic ACTH
Pituitary MRI
Chest CT
Adenoma
Negative
Negative
Positive
Transsphenoidal pituitary resection
Inferior petrosal sinus sampling for ACTH
Treat 1° tumor
Ectopic ACTH
IPS:P>3.0
IPS:P<2.0

Cushings disease



Moon facies and increased supraclavicular fat pads in Cushing's syndrome. 30 year-old woman with Cushing's disease showing round, plethoric "moon" face, facial hirsutism, and increased supraclavicular fat pads. (Reprinted with permission from Williams Textbook of Endocrinology, 8th ed, Foster, DW, Wilson, JD (Eds), WB Saunders, Philadelphia, 1996.)

Indications for medical management:

- Failure of all other treatment modalities
- Preparation for surgery to relieve extreme symptoms
- Interval between RT and development of eucortisolemia

Drugs :

- Ketoconazole
- Aminoglutethimide
- Metyrapone
- Mitotane
- Etomidate
- Mifepristone
- Octreotide

- Ketoconazole: First line drug
  - 17α-hydroxylase, 11β-hydroxylase,18-hydroxylase, and especially 17,20-lyase enzymes are all blocked by ketoconazole
  - 400–1200 mg/d (average 800 mg/d)
  - effective in 70-100%
  - liver toxicity 15%

- Aminoglutethimide

  inhibits the first step in cortisol biosynthesis
  (cholesterol →pregnenolone)

  Effective 50%

  250-2000 mg/day

  Can be given with ketoconazole

- Metyrapone

  Selective inhibitor of 11β-hydroxylase
  Effective in 85%
  doses of 750-2000 mg/d
  Acne, hirsutism

- Mitotane
  - Adrenocorticolytic effects and direct inhibition of steroid synthesis
  - 2-4 g/day
  - Effective in 80%,long term remission in 30%
  - Higher response rate with concomitant pituitary irradiation
  - Contraindicated in women planning for pregnancy within 5 years
  - Side effects : gastrointestinal, hypercholesterolemia,adrenal insufficiency

- Etomidate
  - Life-threatening situations with severe hypercortisolism
  - Oral dosing is contraindicated.
  - Dose of 0.1 mg/kg/h
  - Eucortisolism achieved within 11–48 h by using a continuous infusion

- Mifepristone

  Major vegetative depression, suicidal ideation with hypercortisolism

- Octreotide
  Ectopic ACTH source

Prolactin Function

- Serum prolactin levels (normal 5-20ng / ml)
- Dynamic tests:

not used if prolactin levels > 150ng / ml or tumor is found on MRI / CT

used if prolactin levels are mildly elevated and MRI findings are equivocal

Stimulation tests :

- TRH
- Chlorpromazine
- Metoclopramide

Suppression tests:

- L-dopa
- Nomifensine

Prolactin

- < 25 ng/ ml : normal
- 25-150ng/ml:
  - prolactinoma
  - stalk effect
  - drugs
  - Hypothyroid
- > 150ng/ml : prolactinoma

Hook effect

even large elevations will show normal PRL levels on testing due to large size of molecules. Do serial dilutions

- ELEVATED PROLACTIN LEVELS
- Physiological –
  Pregnancy
  lactation
- Pharmacological –
  psychotropic drugs
  Antihypertensives
  high dose estrogens
- Pathological –
  hypothyroidism
  chronic renal failure
  hepatic diseases
  cushings disease

Prolactinomas

Indications for bromocriptine therapy:

- Non invasive prolactinoma and serum prolactin level 150-500ng/ml
- Serum prolactin level >1000ng/ml
- Residual / recurrent prolactinoma following surgery

Criteria for cure:

- Normal prolactin level
- Asymptomatic
- Negative MRI study for 5 years
- If prolactin level is <100ng/ml and shows no tendency to rise is indicative of stalk damage

Prolactinomas

- Only pituitary tumor for which medical therapy has proven and primary role
- Observation
- Dopamine agonist

  Bromocriptine
  Cabergoline

Dopamine agonist

Selective activation of D2 receptors located on lactotroph cell surface

□

Decrease adenylate cyclase activity

□

Decrease in C- AMP level

□

Inhibition of PRL synthesis and release.

Dopamine agonists:

- Bromocriptine
- Cabergoline.
- Pergolide mesylate
- Lisuride
- Quinagolide

Side effects– GI intolerance, postural hypotension, constipation, nasal stuffiness

Bromocriptine:

- (2-bromo-α-ergocryptine mesylate)
- Developed by Flückiger and colleagues in the late 1960s
- Purpose was inhibiting prolactin secretion without the uterotonic, vasospastic properties of other ergots

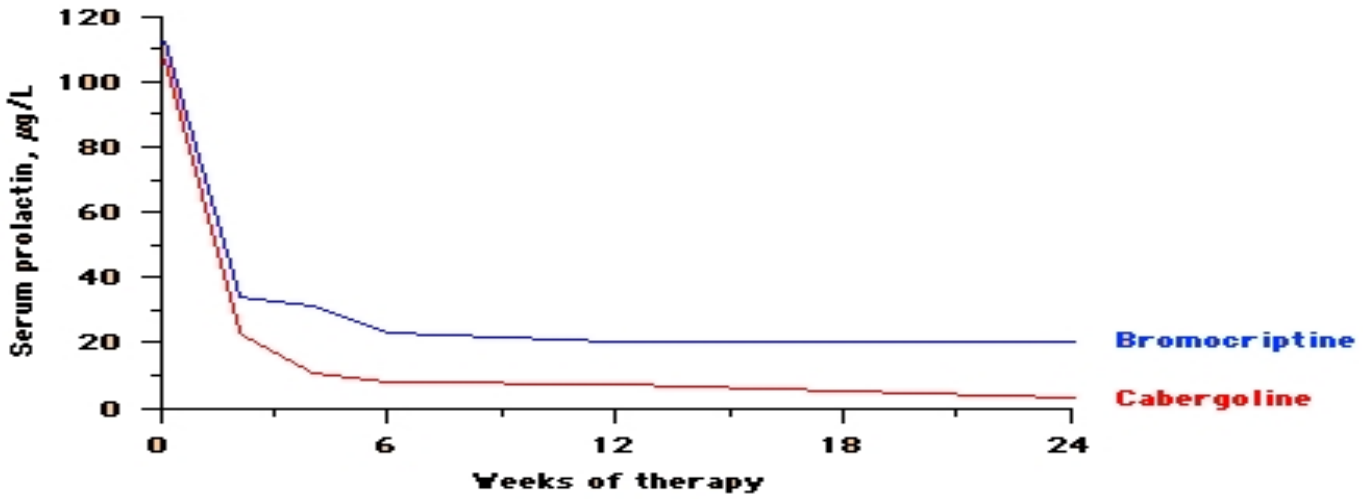
- Serum levels peak after 3 h, and the nadir is observed at 7 h with very little bromocriptine detectable in the circulation after 11-14 h.
- The absorption rate from the GI tract is 25-30%.
- Very high first-pass effect, with 93.6% of a dose being metabolized and only 6.5% of an absorbed dose reaching the systemic circulation unchanged
- Excreted via the biliary route into the feces
- Levels in the fetus about one-fourth of that found in maternal blood
- start low dose at 1.25- 2.5 mg day at night before increasing to 2.5 – 10 mg per day in divided doses
- Take with food to reduce side effects

Cabergoline:

more effective
less side effects than Bromocriptine
more expensive
given once or twice a week with a starting dose of 0.25 mg 2 x week

Titrate these based on prolactin levels and tolerability

Dopamine Agonist Therapy



Dopamine agonist drugs lower serum prolactin concentrations in prolactinoma Serum prolactin concentrations in women with hyperprolactinemic amenorrhea treated with bromocriptine and cabergoline. Both drugs lowered serum prolactin concentrations into the normal range (upper limit of normal equals 20 μg/L). (Data from Webster, J, Piscitelli, MD, Polli, A, et al, N Engl J Med 1994; 331:904.)

Acromegaly

- Somatomedin-C (IGF-1) : always elevated in acromegaly
- GH levels:fasting state and after administration of stimulatory or inhibitory agents

Stimulatory tests :

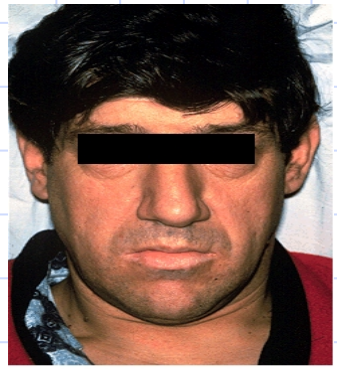
Insulin induced hypoglycemia after IV administration of 0.1-0.15IU/Kg of plain insulin

GH level >5ng / ml indicates normal function

it is avoided in elderly, those with cerebro vascular disorders or convulsive disorder

Oral glucose suppression test: Failure of suppression of elevated levels of GH to < 2ng / ml after 75 gm glucose loading

Acromegaly



Facial features of acromegaly
A man with acromegaly showing the characteristic changes of enlargement of the jaw, nose and frontal bones, and coarse facial features. Courtesy of Verna Wright, MD, FRCP.

Indications :

- Failure of surgery to normalize IGF 1 levels
- Awaiting the beneficial effects of RT
- Unresectable tumors

Drugs :

- Somatostatin analogues
- Dopamine agonists
- GH receptor antagonist - Pegvisomant

Limitations :

- Cost
- Inability of tumor shrinkage sufficient to relieve any mass effect

Somatostatin analogues:

- Octreotide :45 times more potent.
  - half-life in plasma being 113 min
  - peak plasma concentrations within 1 h
  - suppress GH levels for 6–12 h
  - Mechanism of action
    - Inhibit GH secretion
    - partially inhibits GH-induced IGF-1 generation
    - simulates IGF-BP1 expression
    - reduce GHRH release

Clinical improvement-

- headache 84%
- hyperhydrosis 65%
- decrease in ring size in 55%
- improvement in cardiac function and sleep apnea

	Octreotide (S/C) 100 to 500 mic.gm TDS	Octreotide LAR (I/M) at 28 days interval	Lanreotide (I/M) every 7-14 days	Pegvisomant
GH REDUCTION	47%	56%	50%	Not useful
IGF1 REDUCTION	46%	66%	48%	97%

Freda PU:clinical review 150:somatostatin analogs in acromegaly.j clin endocrinol metab 87:3013-3018,2002

Dopamine agonists :

- used both as primary and adjuvent treatment

  Bromocriptine up to 20 mg/day
  Cabergoline 1–2 mg/week

- Response rate low

Dopamine agonists :

	Bromocriptine	Cabergoline
GH REDUCTION	20%	44%
IGF1 REDUCTION	10%	35%

Freda PU:clinical review 150:somatostatin analogs in acromegaly.j clin endocrinol metab 87:3013-3018,2002

GH-Receptor Antagonist :

- Pegvisomant :
- Check IGF 1 level every 4-6 weeks
- Monitoring GH not useful
- Dose 10-40 mg/d

Thyrotropic Function

- T3 , T4 , TSH levels
- If TSH levels are normal in the presence of low T3 / T4 levels then TRH reserve is tested

200 micro grams of TRH is given IV –if TSH is elevated to > 6-20 micro units / ml : normal

absence of response :

total hypophysectomy

Decreased response:

thyroid hormone therapy
glucocorticoid therapy
Hyperthyroidism
renal failure
depression

Thyrotropin secreting adenomas

- Somatostatin analogues:>90% respond
- Dopamine agonists:Bromocriptine:20 % respond

GONDOTROPH FUNCTION

CRITERIA :

- Absence of other hormonal abnormality
- Elevated basal and stimulated response of gonadotropins

DIABETES INSIPIDUS

- Polyuria secondary to water diuresis and poly dipsia
- Due to low levels of ADH
- High output of dilute urine
- Craving for water, especially ice cold water
- Incidence
  9.2% in micro adenoma surgery
  37% in case of total hypophysectomy
- Mostly due to extreme sensitivity of hypothalamic neurohypophyseal unit to local alterations in blood flow, edema and traction on pituitary stalk and is transient
- Permanent disturbance of ADH secretion –direct damage to neuro hypophyseal unit

Types of presentation

- Transient polyuria starting 1□3 days after surgery and lasting for 1□7 days ; local edema and traction on pituitary stalk
- Triphasic response
  polyuria beginning 1□2 days after surgery lasting for 4□5 days
  normalization of urine output / SIADH like water retention 4□5 days
  return of polyuria
- Transient polyuria begining immediate post op
- Permanent polyuria beginning immediate post op and continuing without any interphase

DIAGNOSIS:

- Urine output >250ml/hr (>3ml/kg/hr in pediatric patients)
- Urinary s.g. <1004
- Urinary osmolality <200mosm/kg
- Normal or above normal serum sodium level
- Normal adrenal function

Depends on :

- pts clinical status
- urine volume
- Concentration of serum electrolytes
- creatinine

If alert, with intact thirst, mild DI,

pt can self regulate water intake
DDAVP –nasal spray 2.5micro gm BD

If thirst mechanism is impaired

-meticulous I/o records
-daily wt measurement
-frequent electrolytes , urea , hematocrit
-supplementation of free water
-vasopressin analogues

- If consciousness is impaired
  -hrly I/o, urinary specific gravity
  -4 hrly electrolytes
  -parenteral fluids
  -titrated dosages of desmopressin-2-4microgm IV/SC in 2 divided doses

Chronic DI

- Rare in c/o trans sphenoidal surgery
- Treatment of choice is DDAVP
- Other drugs :
  - clofibrate 500mg 2-4 times/d
  - chlorpropamide –50-500 mg/day
  - carbamazepine 400-600mg/day

SIADH

- Less common
- Causes :

  preop medications

  anaesthetic agents

  surgical stress

  surgical irritation of neurohypophyseal unit

DIAGNOSTIC CRITERIA

- Hyponatremia
- Inappropriately concentrated urine
- No e/o renal /adrenal dysfunction
- Low serum osmolality
- No hypothyroidism
- No e/o dehydration/overhydration

Water load test

- Symptoms –of hypo natremia

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Principal water-electrolytes disorders

		DI	SIADH	CSWS
Etiology		Reduced secretion of ADH	Excessive release of ADH	Release of brain natriuretic factor
Urine	Output	> 30 ml/kg/h		
	specific gravity	< 1.002		
	Sodium	< 15 mEq/l	> 20 mEq/l	> 50 mEq/l
	Osmolality vs. serum osmolality	Lower	Higher	Higher
Serum	Sodium	Hypernatremia	Hyponatremia	Hyponatremia
	Osmolality	Hyperosmolality	Hypoosmolality	
Intravascular volume		Reduced	Normal or increased	Reduced

Abbreviations: ADH, antidiuretic hormone; CSWS, celebral salt-wasting syndrome; DI, Diabetes insipidus; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

sumit Fluid and electrolyte... 00:58

TREATMENT

ACUTE SIADH : fluid restriction 0.5-1.5 litres/day

If sodium levels<120meq/l –hypertonic saline+furosemide diuresis

Correction rate of 0.5meq/hr

CHRONIC SIADH :

long term fluid restriction

demeclocycline 150-300mg q 6hrs

furosemide 40 mg OD

lithium

phenytoin

THANK YOU