PITUITARY ADENOMA
HORMONAL AND MEDICAL MANAGEMENT
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
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

1. Establishing hypercortisolism
2. Distinguishing ACTH-dependent from ACTH independent causes of hypercortisolism
3. 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-hydroxycorticosteroid
- Overnight 8 mg dexamethasone 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
Cushings disease

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

- $17\alpha$-hydroxylase, $11\beta$-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 $\rightarrow$ 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 $<100\text{ng/ml}$ and shows no tendency to rise is indicative of stalk damage
Prolactinomas

- Only pituitary tumor for which medical therapy has a proven 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-\(\alpha\)-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

Titrates these based on prolactin levels and tolerability
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 cerebrovascular 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

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
<table>
<thead>
<tr>
<th></th>
<th>Octreotide (S/C) 100 to 500 mic.gm TDS</th>
<th>Octreotide LAR (I/M) at 28 days interval</th>
<th>Lanreotide (I/M) every 7-14 days</th>
<th>Pegvisomant</th>
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</thead>
<tbody>
<tr>
<td>GH REDUCTION</td>
<td>47%</td>
<td>56%</td>
<td>50%</td>
<td>Not useful</td>
</tr>
<tr>
<td>IGF1 REDUCTION</td>
<td>46%</td>
<td>66%</td>
<td>48%</td>
<td>97%</td>
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Dopamine agonists:

- Used both as primary and adjuvant treatment
  - Bromocriptine up to 20 mg/day
  - Cabergoline 1–2 mg/week
- Response rate low
## Dopamine agonists:

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<tr>
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<td>20%</td>
<td>44%</td>
</tr>
<tr>
<td>IGF1 REDUCTION</td>
<td>10%</td>
<td>35%</td>
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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 beginning 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 2.5 micro 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 hyponatremia
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