



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 μ g/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
- ◆ Corticotroph 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 11 β - 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**

- 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 >1000 ng/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- 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

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

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%
- ◆ hyperhidrosis 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 adjuvant 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% |

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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

GONADOTROPH 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 $>250\text{ml/hr}$ ($>3\text{ml/kg/hr}$ in pediatric patients)
- ◆ Urinary s.g. <1004
- ◆ Urinary osmolality $<200\text{mosm/kg}$
- ◆ 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 hyponatremia

TREATMENT

ACUTE SIADH : fluid restriction 0.5-1.5 litres/day

- If sodium levels < 120 meq/l – hypertonic saline + furosemide diuresis
- Correction rate of 0.5 meq/hr

CHRONIC SIADH :

- long term fluid restriction
- demeclocycline 150-300mg q 6hrs
- furosemide 40 mg OD
- lithium
- phenytoin



THANK YOU