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 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

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 >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 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%
  - 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 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

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 hyponatremia

		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.

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