Surgical Nuances to Managing Cushing’s Disease

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Cortisol Regulation

Cushing’s Syndrome – Excess Cortisol

- Truncal obesity
- Decreased libido
- Hypertension/DM
- Hirsutism
- Plethora/Round Face
- Thin skin
- Weakness
- Growth failure
- Muscle weakness
- Striae
- Acne
- Dorsal (and supra-clavicular) fat pad
- Female balding
- Menstrual changes
- Lethargy/depression
- Osteopenia/osteoporosis
- Recurrent infections
- Easy bruising
Cushing's Syndrome: Major Causes

- Exogenous (iatrogenic)
- ACTH-dependent:
  - Pituitary adenoma (Cushing's disease) 70%
  - Ectopic ACTH Syndrome 15%
- ACTH-independent
  - Adrenal adenoma 10%
  - Adrenal carcinoma 5%

Diagnosis

- 24 hr urine free cortisol
- Dexamethasone suppression test
- Midnight salivary cortisol

Midnight Salivary Cortisol

Salivary cortisol

- Sensitivity: 92%
- Specificity: 95%

- False positives:
  - Stress
  - Sleep disturbances
  - Sample contamination


Raff et al JCEM 83:2681, 1998
Endogenous causes of Cushing’s Syndrome

**ACTH** dependent ACTH independent

**Additional Work-up**

- **ACTH level**
  - <5 pg/ml (ACTH-independent)
    - Adrenal CT
    - Plasma DHEA-S
  - ACTH normal or high (ACTH-dependent)
    - High dose dexamethasone test
    - MRI (dynamic sellar imaging)
    - Inferior petrosal sinus sampling (IPSS)

**MRI of Sella**

- 1.5 or 3T magnet
- Coronal and Sagital thin cuts through sella
- T2 coronal images through sella
- Dynamic Imaging
  - Timed coronal sequences after contrast administration
- Imaging must be reviewed by specialist or neurosurgeon with experience in evaluating sellar MRI scans

**Inferior Petrosal Sinus Sampling**

*Determining source of ACTH*

- Simultaneous measurement of blood from the cavernous sinus/inferior petrosal sinus and peripheral blood
- Positive if central:peripheral ACTH level is >2 at baseline or >3 after CRH stimulation
- Important to review venous anatomy
Dynamic MRI vs. IPSS

- Dynamic MRI was positive in 96.8% of cases with positive pathology (66 cases studied)*
- In patients who had both, dynamic MRI and IPSS, dynamic MRI predicted lateralization of the tumor in 76.9% vs 61.5% of cases.


Cushing’s disease - Therapy

- Endonasal transsphenoidal surgery (complete exploration of gland)
  - Need to expose the entire gland
  - If tumor identified on MRI
    - Adenomectomy
  - If MRI neg
    - Midline vertical incision is made
    - Vertical incisions every 2mm created
    - If tumor found - adenomectomy
  - If exploration is negative - treatment options include:
    - Hemihypophysectomy
    - Total hypophysectomy

Postoperative Management

- Cortisol level obtained the day after surgery
  - 73 pts studied at UCSF*
    - Subnormal postop cortisol – 4% recurrence rate
    - Normal postop cortisol – 22% recurrence rate
  - Patients are maintained on low dose steroids and then monitored by the endocrinologist afterwards
  - Patients cured of their Cushing’s may require 6-12 months of cortisol replacement
    - ACTH axis suppressed in gland (6 months)
    - CRH axis suppressed in hypothalamus (12 months)


54 yo female with Cushing’s Disease

24hr UFC >1000ug/d (nl < 50 ug/d)
Case example:
32 yo female with Cushing’s disease and a 6 mm adenoma

Postoperative cortisol: 0.9 ng/ml

Case Presentation

- 36yo M with facial plethora
  - Patient was convinced something was wrong
  - 6 lb wt loss
- SH
  - Pt works as a stock broker (high stress/early hours)
  - Pt exercises 2 hrs/day

36 yo with Cushing’s disease

32 yo female with Cushing’s disease, MRI read as negative

24hr UFC = 85 ug/d (nl < 50ug/d)
Case Presentation

- Work up
  - 15 24 hr UFC over 2 years, most abnormal, some >500
- ACTH was undetectable and 10 on another reading
- CT of abdomen neg
- NM scan neg
- MRI neg.
- Patient went to NIH
  - Confirmed ACTH dependent Cushing’s

Case presentation

- Patient underwent endonasal transsphenoidal resection of tumor with extracapsular dissection (pseudocapsule)
- Postop cortisol 1 ug/dl
- Pathology confirmed ACTH+ pituitary adenoma
- 11 months postop, pt was weaned off cortisol replacement with AM cortisol 7, post stim – 18.

Case Presentation - MRI

27 yo female with Cushing’s disease

- MRI negative
- IPSS positive,
  - Strong left gradient (>10:1)
  - Symmetrical venous drainage
- Surgical exploration negative
- Patient underwent hemihypophysectomy
- Postop Cortisol 1.4 ug/dl
- Anterior lobe function preserved
45 yo male with Cushing’s Disease

Pediatric Pituitary Adenomas
Relationship between age and pathology

7 yo boy with Cushing’s disease
Persistent Cushing’s Disease

- Repeat imaging studies
  - Consider repeat surgery
  - Medical therapy
  - Gamma knife Radiosurgery
  - 3-D conformal radiotherapy
- If no tumor can be identified/hypercortisolemia persists
  - Laparoscopic bilateral adrenalectomy
    - Need to be cautious of Nelson’s Syndrome
  - Total hypophysectomy

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