Ectopic ACTH Syndrome (EAS)
Epidemiology

- EAS is an uncommon cause of Cushing Syndrome
- Cause of cushing’s syndrome in most cancer pts.
- Male: female 1:1 but men more likely to have EAS as cause of cushing syndrome
Associated Tumors

- Small cell lung CA (50%)
- Bronchial carcinoid tumors (10%)
- Thymic carcinoid/thymoma (10%)
- Pancreatic islet cell tumors (5%)
- Pheochromocytoma (5%)
- Medullary carcinoma (5%)
Definitions

- Cushing’s Disease: cortisol excess caused by pituitary ACTH overexcretion
- Cushing’s Syndrome: cortisol excess by any cause
- ACTH dependent cushing’s syndrome: that caused by ↑ACTH from pituitary or ectopic source
- ACTH independent cushing’s syndrome: that caused by adrenal source
Hypothalamic-Pituitary-Adrenal Axis

- **Hypothalamus**
  - CRH, vasopressin

- **Pituitary**
  - MSH, endorphins
  - POMC
  - ACTH

- **Adrenal**
  - AT I, AT II
  - aldosterone (Na↑, K↓, H↑)
  - cortisol
  - DHEA, DHEAS, Androstenedione

- **Regulatory Factors**
  - Renin
  - Aldosterone
Causes of Cushing’s Syndrome

- Exogenous glucocorticoids (#1 cause)
- ACTH-dependent (80%)
  - Pituitary micro- or macroadenoma
  - ACTH or CRH-producing tumors
- ACTH-independent (20%)
  - Adenoma
  - Carcinoma
  - Adrenal nodular hyperplasia (familial)
Clinical features

- Truncal obesity, buffalo hump, supraclavicular fat pad
- Moon facies
- HTN
- Amenorrhea
- Hirsutism, acne
- Abdominal striae, bruising
- Nonpitting edema
- Hyperpigmentation (if ACTH-dependent)
Clinical Features

- Irritability, mania, depression, psychosis
- Diabetes mellitus (<20%)
- Osteoporosis
- Weakness (proximal muscles) and fatigue
- Leukocytosis
- Hyperlipidemia
Clinical features in EAS

- Typical signs/symptoms of cushing’s syndrome may be minimal
- Sudden onset particularly in rapidly growing SCLC
- Features more common in slower growing tumors (carcinoid or pheo)
- Hypokalemic alkalosis is prominent (rare in cushing’s disease)
Screening for Cushing’s Syndrome

- 24Hr urine free cortisol (>100ug/d)
- Overnight Dexamethasone Suppression (1mg @MN)
  - Failure to suppress 8AM cortisol to <5ug/dl
- Midnight serum cortisol/ACTH
  - Cortisol is highest in early am (4am)
  - Cortisol is lowest in late evening
Pseudo-Cushing’s Syndrome

- Severe Obesity
- PCOS
- Alcoholism
- Depression
- Acute illness
Confirmation of Cushing’s Syndrome

- 48H low dose Dexamethasone Suppression (0.5mg Q6HX48Hr)
  - Failure of urinary cortisol to fall to less than 30ug/d
  - Failure of plasma cortisol to fall to less than 5ug/d
  - Skip if screening tests are markedly positive
Distinguishing the causes of Cushing’s Syndrome

- Tests lack specificity b/c some tumors (especially SCLC) exhibit dramatic changes in excretion of ACTH
- Pituitary microadenoma and EAS are the most difficult causes of Cushing’s syndrome to distinguish
Diagnosing the etiology of Cushing’s Syndrome

- **Plasma ACTH levels**
  - Low in adrenal (ACTH-independent) source
  - Normal/↑ in pituitary adenoma
  - Normal/↑↑↑ in EAS (most>200pg/ml)

- **High dose Dexamethasone suppression (2mg Q6HX48H)**
  - Most pituitary tumors will show suppression of cortisol
  - Failure to suppress urinary free cortisol by >90% is specific for adrenal and ectopic tumors
  - Some carcinoid tumors are suppressible, giving a false + result
Diagnosing the etiology of Cushing’s Syndrome

- CRH + (Vasopressin or Desmopressin) Stimulation test
  - Serum cortisol will ↑>33% in pituitary source
- CRH stimulation/Metyrapone infusion
  - ↑↑ ACTH with pituitary tumor
  - No rise in ACTH with EAS
  - Not cost-effective or specific tests
Diagnosing the etiology of Cushing’s Syndrome

- Imaging:
  - Octreotide scan—not specific for ACTH-secreting tumors
  - MRI brain: detects only 50% of pituitary tumors; 10% of normal subjects have evidence of pituitary adenoma
  - CT abdomen/chest: useful only for tumor localization; must make dx with laboratory means

- Bilateral inferior petrosal sinus sampling
  - ACTH gradient from peripheral blood in pituitary tumors
  - Test of choice in distinguishing pituitary microadenomas from EAS
Diagnosis

**Screening**
- Overnight Dexa
- 24H urine cortisol
  - positive

**Plasma ACTH**
- Extremely high
- High/NL
- low

**EAS**
- CT chest/abdomen

**Cushing’s disease vs. EAS**
- 48H High Dose Dexa
  - suppresion
  - Fail to suppress

**Cushing’s disease**
- MRI brain

**EAS vs. pituitary tumor**
- Inf. Petrosal sampling
  - Gradient
  - No Gradient

**Adrenal tumor**
- CT abdomen

**Octreotide Scan**
- CT chest/abdomen
  - CRH+(dDAVP or desmopressin) stim.
    - Negative
    - Equivocal
    - Positive
Distinguishing Causes of Cushing’s Syndrome

- Pituitary 1999
  - 71 patients with cushing’s syndrome, cause confirmed by biopsy
  - Low ACTH and CT abdomen correctly identifies all patients of adrenal origin
  - Inferior petrosal sinus sampling in pts. With NL/↑ACTH was the best predictive test to differentiate EAS from cushing’s disease (100% sens/specific)
  - High-dose dexamethasone suppression test, metyrapone stimulation test and pituitary MRI were not cost-effective and may be misleading.
Treatment of EAS

- Chemotherapy for SCLC
- Surgery for other tumors
- 16% have no evidence of tumor on imaging studies
  - Periodic imaging as tumor may be small
- Medical Management—may be indicated prior to surgery or in non-surgical pts.
- Bilateral adrenalectomy if above fails
Medical Management

- risk of adrenal insufficiency—need to start concomitant glucocorticoid replacement
- Ketoconazole—suppresses adrenal steroidogenesis
- Metyrapone/Aminoglutethemide (as above)
- Mifepristone—glucocorticoid receptor inhibitor
- Octreotide
Prognosis

- Pts. With SCLC and EAS are more resistant to chemotherapy and have a shorter survival particularly due to opportunistic infections. Overall prognosis is poor.