Cushing syndrome

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_Eunice Kennedy Shriver_ National Institute of Child Health and Human Development
NIH, Bethesda, MD
Cushing syndrome

Exposure of the body to supraphysiologic levels of glucocorticoids (GCs) and their metabolic effects
Although the cause of her disease was never confirmed, she is thought to have had an ACTH-secreting pituitary adenoma that underwent spontaneous apoplexy? Or PPNAD and cyclical CS?
Cushing syndrome

Exogenous (iatrogenic)
- GCs 1st line therapy for autoimmune, malignant, allergic and other disorders

Endogenous
- ACTH-dependent
  - Pituitary adenoma (Cushing disease) or other pituitary pathology
- ACTH-independent
  - Adrenal tumors or hyperplasia
  - Ectopic ACTH and/or CRH production
Definitions

Pituitary hormone-producing cells are members of the family of neuroendocrine cells, similar to those of pancreatic islets, as well as dispersed endocrine cells of the gastrointestinal and respiratory tracts. Over the last two decades, there have been terminology shifts that reflect the potential for malignant behavior of even the most bland of those neuroendocrine neoplasms. They evolved from ‘adenoma’ to ‘tumor’ to recognize the lack of predictability. We therefore propose that neoplasms of adenohypophysial cells be termed ‘pituitary neuroendocrine tumors’.

The proposed change in classification by the Club creates a number of untoward challenges:

(i) Gives tumor a sinister connotation and removes meaningful information on its developmental origin;
(ii) Does not address the distinction between an endocrine cell and a neuroendocrine cell, possibly challenging the hierarchal classification of tumors of the endocrine system;
(iii) Asserts high-risk tumor behavior, despite that being an extremely rare exception for the vast majority of pituitary adenomas;
(iv) Has not addressed where very rare true NETs of the pituitary, sellar, and skull base sit in the proposed classification;
(v) Ignores whether similar terminology should apply to neoplasms in other endocrine organs, e.g., thyroid and adrenal.
## Etiology of Endogenous Cushing

<table>
<thead>
<tr>
<th>Cause</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous/Iatrogenic</td>
<td>Administration of pharmacologic doses of GCs</td>
</tr>
<tr>
<td>ACTH-Dependent CS</td>
<td>Pituitary ACTH secreting tumors</td>
</tr>
<tr>
<td></td>
<td>• ACTH-secreting pituitary adenomas (Cushing disease)</td>
</tr>
<tr>
<td></td>
<td>• ACTH-secreting pituitary carcinomas</td>
</tr>
<tr>
<td></td>
<td>• Pituitary blastomas</td>
</tr>
<tr>
<td>Ectopic ACTH and/or CRH secretion</td>
<td>• Bronchial carcinoids</td>
</tr>
<tr>
<td></td>
<td>• Pancreatic neuroendocrine tumors</td>
</tr>
<tr>
<td></td>
<td>• Thymic carcinoids</td>
</tr>
<tr>
<td></td>
<td>• Other (Medullary thyroid carcinoma, neuroblastoma etc)</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td></td>
</tr>
<tr>
<td>Adrenocortical adenoma</td>
<td></td>
</tr>
<tr>
<td>ACTH-Independent CS</td>
<td>Bilateral adrenocortical hyperplasia (BAH)</td>
</tr>
<tr>
<td></td>
<td>• Micronodular (most nodules &lt; 1cm)</td>
</tr>
<tr>
<td></td>
<td>• Pigmented</td>
</tr>
<tr>
<td></td>
<td>• Primary Pigmented Nodular Adrenocortical Disease (PPNAD) in the context of Carney complex</td>
</tr>
<tr>
<td></td>
<td>• Isolated-PPNAD</td>
</tr>
<tr>
<td></td>
<td>• Isolated Micronodular Adrenocortical Disease (iMAD)</td>
</tr>
<tr>
<td></td>
<td>Macronodular (most nodules &gt; 1cm)</td>
</tr>
<tr>
<td></td>
<td>• Bilateral Macronodematous Hyperplasia (BMAH)</td>
</tr>
<tr>
<td></td>
<td>• Massive Macronodular Adrenocortical Hyperplasia (MMAD)</td>
</tr>
</tbody>
</table>
Epidemiology of Endogenous Cushing

Incidence:
- Endogenous CS: 2 to 5 new cases per million people per year
- 10% in children

Causes of Endogenous CS:
- >7 yo:
  - 75-85% → Cushing disease
  - 15% → Adrenal causes
- <7 yo: Adrenal causes (adenoma, carcinoma, or bilateral hyperplasia) most common
- Ectopic ACTH (CRH) production: extremely rare
Hypothalamic – Pituitary – Adrenal (HPA) axis

Hypothalamus → CRH → Pituitary → ACTH → Cortisol → Adrenals →

DIURNAL CORTISOL – NORMAL

Lacroix A et al. Lancet. 2015
Cushing syndrome and the HPA axis

Lacroix A et al. Lancet. 2015
# Presentation of Cushing syndrome

<table>
<thead>
<tr>
<th>System</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height/Growth</td>
<td>Obesity/Weight gain</td>
</tr>
<tr>
<td></td>
<td>Height deceleration</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Easy bruising</td>
</tr>
<tr>
<td></td>
<td>Striae</td>
</tr>
<tr>
<td></td>
<td>Hirsutism</td>
</tr>
<tr>
<td></td>
<td>Acne</td>
</tr>
<tr>
<td></td>
<td>Abnormal fat distribution</td>
</tr>
<tr>
<td></td>
<td>Facial plethora</td>
</tr>
<tr>
<td></td>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Delayed puberty</td>
</tr>
<tr>
<td></td>
<td>Irregular menses</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Osteopenia and increased fracture risk</td>
</tr>
<tr>
<td></td>
<td>Myopathy</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Increased risk for infections</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>Sleep disorders</td>
</tr>
<tr>
<td></td>
<td>Compulsive behavior</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

- Sleep disorders
- Moodiness, anxiety or depression
- Change in school performance
- Red, round face with acne
- Buffalo hump
- Acanthosis nigricans
- Fine downy hair
- Weight gain
- Striae
- Precocious puberty
- Menstrual irregularity
- Bruising
- Other signs

Keil MF. JCEM. 2013.
Screening for CS

Urinary free cortisol level
Midnight serum or salivary cortisol

ACTH > 29 pg/mL
- MRI pituitary
- CRH or DDAVP test
- High dose (120 mcg x weight in kg, max 8mg) dexamethasone suppression test

ACTH < 5 pg/mL

Intermediate ACTH
- CRH or DDAVP test
- High dose (120mcg/kg, max 8mg) dexamethasone suppression test
- Liddle’s test

Confirmation of CS
(Consider repeating another test if high suspicion of CS or following the patient in 6 months if symptoms persist)

Consistent with pituitary source

Bilateral Inferior Petrosal sinus sampling (BIPSS)
- No gradient of ACTH levels
- Imaging studies to identify ectopic source
- Transsphenoidal surgery

Adrenal CT
- Normal or micronodules
- Liddle’s test
- Paradoxical response consistent with PPNAD or iMAD
- Bilateral adrenalectomy

Unilateral tumor
- MMAD or BMAH
- Adrenocortical adenoma (ACA)
- Adrenocortical carcinoma (ACC)

Bilateral adrenalectomy
- Surgical resection
- Surgical resection and/or chemotherapy

Abnormal

Consistent with pituitary source

Measure ACTH

Surgical resection
New consensus guidelines from Pituitary Society

Consensus on diagnosis and management of Cushing’s disease: a guideline update


Lancet Diabetes Endocrinol 2021
Who should be tested

3.1 We recommend obtaining a thorough drug history to exclude exogenous glucocorticoid exposure leading to iatrogenic Cushing’s syndrome before conducting biochemical testing (1➋➋➋➋➋).

3.2 We recommend testing for Cushing’s syndrome in the following groups:

- Patients with unusual features for age (e.g. osteoporosis, hypertension) (Table 1) (1➋➋➋➋➋)
- Patients with multiple and progressive features, particularly those that are more predictive of Cushing’s syndrome (Table 1) (1➋➋➋➋➋)
- Children with decreasing height percentile and increasing weight (1➋➋➋➋➋)
- Patients with adrenal incidentaloma compatible with adenoma (1➋➋➋➋➋).

3.3 We recommend against widespread testing for Cushing’s syndrome in any other patient group (1➋➋➋➋➋).

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**TABLE 1. Overlapping conditions and clinical features of Cushing’s syndrome**

<table>
<thead>
<tr>
<th>Symptoms that best discriminate Cushing’s syndrome (most do not have a high sensitivity)</th>
<th>Signs</th>
<th>Overlapping conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy bruising</td>
<td>Facial plethora</td>
<td>Hypertension*(a)</td>
</tr>
<tr>
<td>Proximal myopathy (or proximal muscle weakness)</td>
<td>Striae (especially if reddish purple and &gt;1 cm wide)</td>
<td>Incidental adrenal mass</td>
</tr>
<tr>
<td>In children, weight gain with decreasing growth velocity</td>
<td></td>
<td>Vertebral osteoporosis*(a)</td>
</tr>
</tbody>
</table>

Cushing’s syndrome features in the general population that are common and/or less discriminatory

- Depression
- Fatigue
- Weight gain
- Back pain
- Changes in appetite
- Decreased concentration
- Decreased libido
- Impaired memory (especially short term)
- Insomnia
- Irritability
- Menstrual abnormalities
- In children, slow growth

- Dorsocervical fat pad (“buffalo hump”)
- Facial fullness
- Obesity
- Supraciliary fullness
- Thin skin*(b)
- Peripheral edema
- Acne
- Hirsutism or female balding
- Poor skin healing
- In children, abnormal genital virilization
- In children, short stature
- In children, pseudoprecocious puberty or delayed puberty
- Incidental adrenal mass
- Vertebral osteoporosis*(a)
- Polyoviscous ovary syndrome
- Type 2 diabetes*(a)
- Hypokalemia
- Kidney stones
- Unusual infections

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Nieman L et al. JCEM. 2008
Tips on choosing the appropriate test

Panel 1: Clinical considerations and recommendations for Cushing's syndrome diagnosis and monitoring of Cushing's disease recurrence

If Cushing's syndrome is suspected:
- Start with urinary-free cortisol (UFC), late-night salivary cortisol (LNSC), or both; dexamethasone suppression test (DST) could also be an option if LNSC not feasible
- Multiple LNSC might be easier for patient collection

If confirming Cushing's syndrome:
- Can use any test
- UFC average two-to-three collections
- LNSC (two or more tests)
- DST useful in shift workers, not in women on oestrogen-containing oral contraceptives
- Measuring dexamethasone concentration, with cortisol concentration, the morning after 1 mg dexamethasone ingestion improves test interpretability

If Cushing's syndrome due to adrenal tumour is suspected:
- Start with DST
- LNSC has lower specificity in these patients

Monitoring for recurrence:
- Consider which tests were abnormal at initial diagnosis
- LNSC most sensitive, should be done annually
- DST and UFC usually become abnormal after LNSC
- UFC is usually the last to become abnormal
Screening for Cushing syndrome

1. Elevated midnight cortisol (salivary or serum)

2. Elevated 24h Urinary Free Cortisol

3. Abnormal response to dexamethasone
Screening for Cushing syndrome

1. Elevated midnight cortisol (salivary recommended at screening)

Salivary
- Collect 2-3 days
- Close to bedtime

Serum
Collection (have an IV at least 3 hours prior and be at bed by 9):
- 11:30pm and 12am: Cortisol and ACTH
- 7:30am and 8am: Cortisol and ACTH

Abnormal response:
- Adults > 7.5mcg/dL (1.8mcg/dL)
- Children > 4.4 mcg/dL

Special considerations:
- Travel from different time zone
- Shift workers
- Salivary cortisol affected by 11-β-HSD2 (avoid tobacco, smoking and licorice the day of the test)
Screening for Cushing syndrome

2. Elevated 24h Urinary Free Cortisol

**Collection:**
Average 2-3 24h collection
Measure urine creatinine
Ensure appropriate urine volume

**Abnormal response:** Use assay specific cut-offs

**Special considerations:**
- Assay used
- High fluid intake
- Sodium intake
- Severe obesity
- Renal failure
- Strenuous exercise
- Adjust for BSA or use of adult cut-offs

Batista DL et al., Pediatrics 2007; 120:e575-86
Screening for Cushing syndrome

3. Abnormal response to dexamethasone

Collection:
- 1 mg (pediatric 15mcg/kg, max 1mg) overnight dexamethasone (Dex administered at 11pm → Cortisol measured next morning at 8am)
- Long low-dose DST (0.5mg Q6H x 48H)
- Doses should be adjusted for children

Abnormal response:
Serum cortisol > 1.8 mcg/dL

Special considerations:
- Measure dex level

Stop OCPs for 6 weeks prior to testing

Nieman L et al. JCEM. 2008
Physiologic/non-neoplastic hypercortisolism (previously known as pseudo-Cushing)

• **Causes**
  - Depression/neuropsychiatric disease
  - Severe obesity
  - Uncontrolled diabetes
  - Glucocorticoid resistance
  - Alcoholism and alcohol withdrawal
  - Renal failure
  (Anorexia nervosa, pregnancy, intense chronic exercise, OSA, MS)

• **Labs**
  - DST, LNSC, and UFC can all show positive (abnormal) results
  - Usually UFC <x3 ULN
  - Dex-CRH
  - DDAVP stimulation test

• **Management**
  - Monitor for 3–6 months
  - Treatment of the underlying condition
  (such as depression)
Physiologic/non-neoplastic hypercortisolism (previously known as pseudo-Cushing)

Dex-CRH test

- Dexamethasone Q6h x 48H
- Then CRH stimulation test
- Measure Cortisol at +15minutes

<table>
<thead>
<tr>
<th>Cutoff cortisol value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.4</td>
<td>100%</td>
<td>55%</td>
</tr>
<tr>
<td>&gt;3.2</td>
<td>91%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Fig 5.—Criteria for best-diagnostic accuracy for dexamethasone–corticotropin-releasing hormone (CRH) test; plasma cortisol levels obtained 15 minutes after administration of CRH. Definition of symbols as in Fig 1. Horizontal rule indicates criterion level.
DDAVP stim test for physiologic/non-neoplastic hypercortisolism

**Background:** Corticotropinomas express V1b receptors or ectopic V2 receptors

**Endogenous Cushing syndrome vs pseudo-Cushing**

- 10mcg of DDAVP as an IV push over 30 seconds
- Collect ACTH and cortisol samples at -15, 0, 15, 30, 45, 60

Endogenous CS (vs pseudoCushing) if ΔACTH >27 pg/mL

### Adverse reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Cold sensation</td>
</tr>
<tr>
<td>Flushing</td>
<td>Increased respiratory rate</td>
</tr>
<tr>
<td>Headache</td>
<td>Water intoxication</td>
</tr>
<tr>
<td>Palpitations</td>
<td>If unrestricted water intake → hyponatremia</td>
</tr>
<tr>
<td>Increase or decrease of blood pressure</td>
<td></td>
</tr>
<tr>
<td>Theoretical risk for increased thrombosis</td>
<td></td>
</tr>
</tbody>
</table>

### Contraindications

- History of thromboembolic disease
- Symptomatic coronary disease
- Critical conditions due to severe hypercortisolism (as considered by the PI or other AIs)

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1. Moro et al. JCEM, 2000
2. Tsagarakis. JCEM. 200
Differential Diagnosis:
ACTH-dependent vs ACTH-independent

- ACTH > 29 pg/mL
  - MRI pituitary
  - CRH or DDAVP test
  - High dose (120 mcg x weight in kg, max 8mg) dexamethasone suppression test
  - Intermediate ACTH
    - Results inconclusive
      - Bilateral inferior petrosal sinus sampling (BIPSS)
        - No gradient of ACTH levels
          - Imaging studies to identify ectopic source
            - Transsphenoidal surgery
              - Consistent with pituitary source
  - Consistent with pituitary source
  - Transsphenoidal surgery

- ACTH <5 pg/mL
  - Adrenal CT
    - Normal or micronodules
    - Bilateral macronodules
      - Liddle's test
        - Paradoxical response consistent with PPNAD or iMAD
          - Bilateral adrenalectomy
            - MMAD or BMAH
              - Adrenocortical adenoma (ACA)
                - Surgical resection
                  - Adrenocortical carcinoma (ACC)
                    - Surgical resection and/or chemotherapy

- Consistent with pituitary source
- Results inconclusive

Midnight serum or salivary cortisol

Consensus with pituitary source
Abnormal

Confirmation of CS
(use another screening test and exclude physiologic/non-neoplastic hypercortisolism)

Differential Diagnosis:
ACTH-dependent vs ACTH-independent

Tatsi C, Stratakis CA. PER. 2019
ACTH-dependent Cushing syndrome
Differential Diagnosis:
ACTH-dependent sources of Cushing's syndrome

ACTH > 29 pg/mL

- MRI pituitary
- CRH or DDAVP test
- High dose (120 mcg x weight in kg, max 8mg) dexamethasone suppression test

- MRI pituitary
- CRH or DDAVP test
- High dose (120 mcg x weight in kg, max 8mg) dexamethasone suppression test

Results inconclusive
- Bilateral Inferior Petrosal sinus sampling (BIPSS)
- No gradient of ACTH levels
- Imaging studies to identify ectopic source
- Transsphenoidal surgery
- Surgical resection

Consistent with pituitary source

- MRI pituitary
- CRH or DDAVP test
- High dose (120 mcg x weight in kg, max 8mg) dexamethasone suppression test

Confirmation of CS
- Use another screening test

ACTH-dependent CS

- Pituitary ACTH secreting tumors
  - ACTH-secreting pituitary adenomas (Cushing disease)
  - ACTH-secreting pituitary carcinomas
  - Pituitary blastomas

- Ectopic ACTH and/or CRH secretion
  - Bronchial carcinoids
  - Pancreatic neuroendocrine tumors
  - Thymic carcinoids
  - Other (Medullary thyroid carcinoma, neuroblastoma etc)

Pituitary ACTH secreting tumors

- ACTH-secreting pituitary adenomas (Cushing disease)
- ACTH-secreting pituitary carcinomas
- Pituitary blastomas

Ectopic ACTH and/or CRH secretion

- Bronchial carcinoids
- Pancreatic neuroendocrine tumors
- Thymic carcinoids
- Other (Medullary thyroid carcinoma, neuroblastoma etc)

Paradoxical response consistent with PPNAD or iMAD

Liddle’s test

Midnight serum or salivary cortisol

Transsphenoidal surgery

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Adrenocortical carcinoma (ACC)

Bilateral adrenalectomy

Adrenocortical adenoma (ACA)

Bilateral adrenalectomy

MMAD or BMAH

Paradoxical response consistent with PPNAD or iMAD

Unilateral tumor

Abnormal

Consider repeating another test if high suspicion of CS or following the patient in 6 months if symptoms persist

Contracted hypercortisolemia

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

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Surgical resection and/or chemotherapy

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Confirmation of CS
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Surgical resection and/or chemotherapy

Abnormal

Bilateral adrenalectomy

Confirmation of CS
- Use another screening test

Surgical resection and/or chemotherapy

Abnormal
Aggressive pituitary tumors (APTs)
Pituitary carcinomas (PCs)

**Aggressive pituitary tumors**
- Local invasion of surrounding tissues
- Increased risk for multiple recurrence
- Rapid tumor growth, or
- Resistance to standard therapies
- May also have certain histological characteristics, which are used to predict their aggressive nature:
  - Ki-67 ≥ 3%
  - Increased mitoses
  - Increased p53 expression

**Pituitary carcinomas**
Definition: non-contiguous distal CNS or other metastases

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Biochemical Hormone excess</th>
<th>Gender Predisposition</th>
<th>Main genetic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giant Prolactinomas</td>
<td>Prolactin</td>
<td>Male</td>
<td>MEN1, AIP</td>
</tr>
<tr>
<td>Giant somatotropinoma</td>
<td>GH</td>
<td>Male</td>
<td>AIP, MEN1, X-LAG</td>
</tr>
<tr>
<td>Crooke’s cell adenoma</td>
<td>ACTH</td>
<td>Any</td>
<td>Unknown</td>
</tr>
<tr>
<td>Silent corticotroph adenoma</td>
<td>None</td>
<td>Any</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pituitary Carcinoma</td>
<td>Variable</td>
<td>Any</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

In an ESE survey, APTs were similar to PCs in terms of their clinical and histological presentation, making it credible to assume that APTs are invasive PitNETs with malignant potential.
Pituitary blastomas

**Diagnosis:** histological

**Presentation:** ACTH-dependent CS in infancy

**Cause:** Germline or somatic *DICER1* gene mutation

Germline mutations of the *DICER1* gene cause the pleuropulmonary blastoma familial tumor and dysplasia syndrome, which involves the presence of multiple benign and malignant tumors in addition to pituitary blastomas.

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Sex</th>
<th>Cause</th>
<th>Presenting findings</th>
<th>Underlying disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 months</td>
<td>Female</td>
<td>Pituitary blastoma (2 x 2 x 3 cm)</td>
<td>Obesity, papilledema, round face, buffalo humo</td>
<td>DICER1 germline and somatic mutations identified</td>
</tr>
<tr>
<td>12 months</td>
<td>Female</td>
<td>Pituitary blastoma (4 x 4 x 6 cm)</td>
<td>Di, short stature, low weight, cushingoid face</td>
<td>DICER1 germline and somatic mutations identified</td>
</tr>
<tr>
<td>8 months</td>
<td>Male</td>
<td>Pituitary blastoma</td>
<td>Weight gain, round face, acne, hypertension, atrophy of the optic discs</td>
<td>DICER1 gene not tested</td>
</tr>
<tr>
<td>18 months</td>
<td>Female</td>
<td>Pituitary blastoma</td>
<td>Weight gain, height deceleration, fatigue, acne, round face, hypertrihosis, hypertension</td>
<td>DICER1 germline and somatic mutations identified</td>
</tr>
<tr>
<td>8 months</td>
<td>Male</td>
<td>Pituitary blastoma</td>
<td>CS</td>
<td></td>
</tr>
<tr>
<td>9 months</td>
<td>Female</td>
<td>Pituitary blastoma</td>
<td>Strabismus, elevated ICP, &quot;plump&quot;</td>
<td>DICER1 somatic LOH identified, but no germline mutation</td>
</tr>
<tr>
<td>9 months</td>
<td>Male</td>
<td>Pituitary blastoma (3 x 2.3 x 1.6 cm)</td>
<td>Ophthalmoplegia and right proptosis, elevated ACTH/cortisol</td>
<td>DICER1 germline mutation identified, tumor not available</td>
</tr>
<tr>
<td>13 months</td>
<td>Female</td>
<td>Pituitary blastoma (2.1 x 1.8 cm)</td>
<td>Right ophthalmoplegia and proptosis, ACTH not measured</td>
<td>DICER1 germline and somatic mutations identified</td>
</tr>
<tr>
<td>24 months</td>
<td>Female</td>
<td>Pituitary blastoma (4cm)</td>
<td>Strabismus, decreased visual accuity, elevated ACTH</td>
<td>DICER1 germline mutation identified but no tumor mutation/LOH</td>
</tr>
<tr>
<td>13 months</td>
<td>Female</td>
<td>Pituitary blastoma (3.5cm)</td>
<td>CS and DI</td>
<td>DICER1 somatic mutation identified, blood not available</td>
</tr>
<tr>
<td>11 months</td>
<td>Male</td>
<td>Pituitary blastoma</td>
<td>Obesity, acne, round face, hypertension</td>
<td>Congenital pulmonary and renal cysts, DICER1 gene not tested but presentation consistent with DICER1 syndrome</td>
</tr>
</tbody>
</table>
Ectopic Cushing syndrome

Sources

- Bronchial carcinoids
- Pancreatic NETs
- Thymic carcinoids
- Ganglioneuroblastoma
- Neuroblastoma
- Wilm’s tumors
- Hepatoblastomas
- Ewing’s sarcoma

Many ectopic tumor stain positive and/or secrete CRH → Pituitary hyperplasia

More et al. JCEM. 2011
Karageorgiadis et al. JCEM. 2015
Differential Diagnosis:
ACTH-dependent sources of Cushing

**When suspecting CD:**
- Pituitary MRI (be aware of incidentalomas!)
- CRH or DDAVP test
- High dose dex suppression
- Abdominal CT (to rule out other adrenal causes of Cushing and confirm bilateral adrenal hyperplasia)
Pituitary MRI

Question about younger population?
Pituitary MRI

Protocol

- Thin sections (1mm) with and without contrast (gadolinium)
- SPGR
- 3T/7T if available

- Typical presentation: microadenomas hypoenhancing after contrast administration

- Positive MRI: 63% of children with CD (50 of 80; 95% CI: 51%–73%).

Batista DL et al. JCEM 2005

OR (95% C.I.)
MRI positive vs negative: OR: 2.6 (1.17 - 5.9)
Adrenal CT
Differentiating pituitary vs ectopic CS

**CRH stimulation test**

- Suggestive of Pituitary source if Cortisol increase (baseline to 30-45min average) >20% and ACTH increase (baseline to 15-30min average) >35%

**DDAVP stimulation test**

- 10mcg of DDAVP as an IV push over 30 seconds
- Collect ACTH and cortisol samples at -15, 0, 15, 30, 45, 60

Pituitary source of CS if %ΔACTH >50% and/or %ΔCort >20% (New cutoff suggested by Frete et al. Non-invasive Diagnostic Strategy in ACTH-dependent Cushing’s Syndrome. JCEM- %ΔCort>18% and %ΔACTH >33%)

Caveat: May appear similar to CD in healthy individuals
Non-invasive pathway....

A non-invasive alternative using high-dose DST and CRH stimulation test predicts Cushing’s disease if both tests are positive. However, if tests are discordant, IPSS is necessary (low quality, discretionary recommendation). Emerging data suggest that CRH and desmopressin testing with pituitary MRI followed by whole-body CT scan might be a reliable alternative, if assessed by an experienced multidisciplinary team (very low quality, discretionary recommendation).

High dose dex suppression

Suggestive of pituitary source if cortisol suppression compared to baseline >69%
**Differential Diagnosis:**

**ACTH-dependent sources of Cushing**

- **ACTH > 29 pg/mL**
  - MRI pituitary
  - CRH test
  - High dose (120 mcg x weight in kg, max 8mg) dexamethasone suppression test

- **Intermediate ACTH**
  - Consider CRH test
  - High dose (120 mcg/kg, max 8mg) dexamethasone suppression test
  - Liddle’s test

- **ACTH <5 pg/mL**
  - Consider repeating another test if high suspicion of CS or following the patient in 6 months if symptoms persist

**Confirmation of CS**
- Use another screening test to exclude physiologic/non-neoplastic hypercortisolism

**When suspecting CD:**
- Pituitary MRI
- CRH or DDAVP test
- High dose dex suppression

**If any of those inconclusive → BIPSS (Inferior Petrosal Sinus Sampling)**

- Consistent with pituitary source
- Results inconclusive
- Bilateral Inferior Petrosal sinus sampling (BIPSS)
- No gradient of ACTH levels
- Imaging studies to identify ectopic source
- Surgical resection
- Transsphenoidal surgery

**Abnormal**
- Adrenal CT
  - Normal or micronodules
  - Liddle’s test
  - Paradoxical response consistent with PPNAD or iMAD

- Bilateral macronodules
- Unilateral tumor
- Adrenocortical adenoma (ACA)
- Adrenocortical carcinoma (ACC)

**Consistent with pituitary source**
- Surgical resection and/or chemotherapy
- Bilateral adrenalectomy

**Confirmation of CS**
- Use another screening test to exclude physiologic/non-neoplastic hypercortisolism

- Surgical resection
- Surgical resection and/or chemotherapy

- Abnormal

Tatsi C, Stratakis CA. PER. 2019
Petrosal Sinus Sampling in Pediatric CD

• Lateralization of ACTH gradient in BIPSS is poor predictor of site of adenoma

• Localization of microadenoma by BIPSS agreed with surgical localization only 58% of cases
ACTH-independent Cushing syndrome
When suspecting Adrenal disorder:
- CT abdomen (better than MRI)
- Liddle’s test (low and high dose dex suppression test)
  - Paradoxical increase in 17OHS/UFC is almost pathognomonic for PPNAD or iMAD

Screening for CS
- Urinary free cortisol level
- Midnight serum or salivary cortisol

Measure ACTH
- ACTH > 29 pg/mL
  - Intermediate ACTH
    - ACTH < 5 pg/mL
      - Adrenal CT
        - Bilateral macronodules
          - Liddle’s test
            - Paradoxical response consistent with PPNAD or iMAD
              - Bilateral adrenalectomy
        - Bilateral adrenalectomy
      - Bilateral micronodules
        - Liddle’s test
          - Paradoxical increase in 17OHS/UFC is almost pathognomonic for PPNAD or iMAD
          - Bilateral adrenalectomy
    - ACTH < 5 pg/mL
      - Adrenal CT
      - Bilateral macronodules
      - Unilateral tumor

Confirmation of CS (use another screening test and exclude physiologic/ non-neoplastic hypercortisolism)
- Consider repeating another test if high suspicion of CS or following the patient in 6 months if symptoms persist
Adrenal CS

Approximately 10% - 15% of CS overall
More common if diagnosis in infants or young children

Causes:

- Adrenocortical tumors (ACT)
  - CS in 1/3 cases (may present with hyperandrogenemia)
  - TP53 (70% of ACTs) / Li-Fraumeni syndrome (AD with early onset ACTs, osteosarcoma, soft tissue sarcoma, breast cancer, brain tumors, leukemia, and others)

- Bilateral adrenocortical hyperplasias (BAH)
  - Macronodular (nodules with diameter greater than 1 cm)
    - Massive macronodular adrenal hyperplasia: ARMC5 gene defects
    - Bilateral macroadenomatous hyperplasia
  - Micronodular (nodules with diameter less than 1 cm)
    - Primary pigmented nodular adrenocortical hyperplasia (PPNAD)- Carney complex: PRKAR1A gene defects
    - (nonpigmented) Isolated micronodular adrenocortical disease (iMAD)
Carney complex

Rare autosomal dominant multiple neoplasia syndrome

“Complex of myxomas, spotty skin pigmentation and endocrine overactivity”

<table>
<thead>
<tr>
<th>Main Criteria</th>
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<tbody>
<tr>
<td>Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)</td>
</tr>
<tr>
<td>Myxoma (cutaneous and mucosal)**</td>
</tr>
<tr>
<td>Cardiac myxoma**</td>
</tr>
<tr>
<td>Breast myxomatosis** or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis</td>
</tr>
<tr>
<td>PPNAD** or paradoxical positive response of urinary glucocorticosteriods to dexamethasone administration during 6-day modified Liddle test</td>
</tr>
<tr>
<td>Acromegaly due to GH-producing adenoma**</td>
</tr>
<tr>
<td>TCCSCT** or characteristic calcification on testicular ultrasonography</td>
</tr>
<tr>
<td>Thyroid carcinoma** or multiple, hypoechoic nodules on thyroid ultrasonography</td>
</tr>
<tr>
<td>Psammomatous melanotic schwannoma**</td>
</tr>
<tr>
<td>Blue nevus, epithelioid blue nevus (multiple)**</td>
</tr>
<tr>
<td>Breast ductal adenoma (multiple)</td>
</tr>
<tr>
<td>Osteochondromyxoma of bone**</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Supplemental criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected 1st-degree relative</td>
</tr>
<tr>
<td>Inactivating mutation of the PRKAR1A gene</td>
</tr>
</tbody>
</table>

*To make a diagnosis of Carney complex, a patient must either: 1) exhibit 2 of the manifestations of the disease listed above, or 2) exhibit one of these manifestations and meet one of the supplemental criteria (an affected first-degree relative or an inactivating mutation of the PRKAR1A gene); **with histologic confirmation
Molecular basis of CNC

- CNC1 locus, chr 17q24, **PRKAR1A**: 70-80%
- CNC2 locus, chr 2p16
- Other: **PRKACB**, unknown
PPNAD in Carney complex

- Most common endocrine manifestation of Carney complex
- Up to 60% of all patients
- Histological evidence found in almost every patient with CNC who underwent an autopsy

- May be periodic (episodic/cyclical) and atypical CS
- May present in asthenic patients (rather than obese)
Liddle’s test in PPNAD

- 2 days baseline urine collection
- 2 days of Q6h low dose dexamethasone (start at 6am)
- 2 days of Q6h high dose dexamethasone (start at 6am)
- 24h urine collection
- Measure cortisol/ACTH/dex on day 3(5) and 5(7)
- Increase of UFC by >50% on day 6 vs baseline

Circles represent patients with primary pigmented nodular adrenocortical disease, squares represent patients with macronodular adrenocortical disease, and triangles represent patients with single adenomas.

Treatment
Treatment of Cushing syndrome

First line → Surgical approach

- Transsphenoidal resection

- Adrenal tumor resection, unilateral/bilateral adrenalectomy
Post-TSS follow up

• Monitor for remission of Cushing
  • Serial Cortisol/ACTH
  • Cortisol <2 mcg/dL sign of remission

• Monitor for signs of adrenal insufficiency (CD)
  • Start dexamethasone when necessary
  → Transition to HC on discharge

Tatsi C et al. Under review
Post-TSS follow up

- Monitor for water balance problems
  - DI, SIADH, triphasic
  - Strict I/Os, acute care panel Q6hours, UA SG Qvoid

- Other post-operative complications
  - Central hypothyroidism
  - Growth hormone deficiency
  - Hypogonadism
  - Bleeding
  - Infection (meningitis)
  - Pituitary apoplexy

- Mortality rate <1%
Pituitary Radiation

• Second-line treatment after surgical treatment in Cushing’s disease failed
  • Hypopituitarism is the most common side effect

• > 80% of patients will have remission after irradiation of the pituitary gland

Types
• Conventional RT small radiation doses are given on a number of occasions for a cumulative dose of 45–50 Gy
  • Stereotactic radiotherapy can be given on a single occasion or fractionated on several occasions.
    (photon therapy, gamma knife)

Follow-up intervals in Cushing’s disease patients after radiation therapy
March 2020: Isturisa (osilodrostat), blocks 11-beta-hydroxylase
Thank you
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