Cushing syndrome

Authors: Dr. Noel Somasundaram, Dr. Henry Rajaratnam, Prof. Chandrika Wijeyaratne, Dr. Prasad Katulanda, Dr. Uditha Bulugahapitiya, Dr. Sajith Siyambalapitiya, Dr. Charles Antonypillai, Dr. Manilka Sumanathilake, Dr. Chaminda Garusinghe, Dr. Dimuthu Muthukuda, Dr. M. W. S. Niranjala, Dr. Kavinga Gunawardena, Dr. Nayananjani Karunasena, Dr. W. S. T. Swarnasri, Dr. M. Aravinthan, Dr. D. C. Kottahachchi, Dr. N. A. S. Ariyawansa, Dr. L. D. Ranasinghe, Dr. K. D. Liyanarachchi

Introduction

Cushing syndrome (CS) comprises symptoms and signs associated with prolonged exposure to inappropriately elevated levels of free plasma glucocorticoids. Iatrogenic CS is the most common form. Endogenous CS, may be caused by either excess ACTH secretion or independent adrenal overproduction of cortisol.

Epidemiology

Endogenous CS is a very rare entity, with an annual incidence of 2-3 cases per million individuals. The female: male ratio is 3:1. In patients whom initial cure was not obtained, a 2 to 3 fold increase in mortality is reported.

Clinical features of CS

CS often presents a diagnostic challenge, particularly in the early stages when the signs and symptoms are non-specific. As the clinical features are non-specific, presence of highly discriminative clinical features (Table 1) should prompt further biochemical tests.

List of abbreviations

ACTH Adreno Cortico Trophic Hormone
BIPPS Bilateral Inferior Petrosal Sinus Sampling
CS Cushing Syndrome
CD Cushing Disease
HDDST High Dose Dexamethasone Suppression Test
HPA AXIS Hypothalamo Pituitary Adrenal Axis
LDDST Low Dose Dexamethasone Suppression Test
ODST Overnight Dexamethasone Suppression Test
UFC Urine Free Cortisol
GFR Glomerular Filtration Rate
CRH Corticotropin Releasing Hormone
PCOS Polycystic Ovary Syndrome
TSS Transphenoidal Surgery
Table 1. Highly discriminative features of CS

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>% of patients</th>
<th>Discriminative index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy bruising</td>
<td>62%</td>
<td>10.3</td>
</tr>
<tr>
<td>Proximal muscle weakness</td>
<td>56%</td>
<td>8</td>
</tr>
<tr>
<td>Facial plethora</td>
<td>94%</td>
<td>3</td>
</tr>
<tr>
<td>Striae (esp. reddish purple and &gt;1 cm wide)</td>
<td>56%</td>
<td>2.5</td>
</tr>
</tbody>
</table>

In children: weight gain with decreasing growth velocity

Table 2. Less discriminative clinical features of CS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Overlapping conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>Dorso-cervical fat pad</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Depression</td>
<td>Facial fullness</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Obesity</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Back pain</td>
<td>Supra clavicular fullness</td>
<td>PCOS</td>
</tr>
<tr>
<td>Decreased concentration</td>
<td>Thin skin</td>
<td>Hypokalaemia</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>Peripheral oedema</td>
<td>Renal calculi</td>
</tr>
<tr>
<td>Impaired memory</td>
<td>Acne, hirsutism and female balding</td>
<td>Unusual infection</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Poor skin healing</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>In children – short stature</td>
<td></td>
</tr>
<tr>
<td>Menstrual abnormalities</td>
<td>Abnormal genital virilization</td>
<td></td>
</tr>
<tr>
<td>Slow growth – children</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Classification of CS

Based on etiology, CS is broadly classified into three groups as outlined in table 3.

Table 3. Classification of CS

<table>
<thead>
<tr>
<th>ACTH Dependent</th>
<th>ACTH Independent</th>
<th>Pseudo-Cushing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing disease (pituitary)</td>
<td>Adrenal adenoma and carcinoma</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Ectopic ACTH syndrome</td>
<td>Primary pigmented nodular adrenal hyperplasia and Carney syndrome</td>
<td>Depression</td>
</tr>
<tr>
<td>Ectopic CRH syndrome</td>
<td>McCune-Albright syndrome</td>
<td>Obesity</td>
</tr>
<tr>
<td>Macronodular adrenal hyperplasia</td>
<td>Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1α)</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic (treatment with ACTH)</td>
<td>Iatrogenic (steroids)</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis of Cushing syndrome (CS)

After exclusion of iatrogenic CS, further investigations are recommended in following groups.

- Patients with multiple and progressive features, particularly features which are more predictive of CS
- Patients with adrenal incidentaloma
- Patients with unusual features for age (e.g. osteoporosis, hypertension)
- Children with decreasing height velocity and increasing weight (investigations for CS is not considered in obese children unless their linear growth is retarded)

Initial investigations

Patients with high pre-test probability should be considered for investigations. One of the four highly sensitive screening tests should be used as the initial investigation, based on the suitability for a given patient.

1. 1mg overnight dexamethasone suppression test (ODST)
2. Low dose dexamethasone suppression test (LDDST 2 mg/day for 48 h)
3. Urine free cortisol (UFC; at least two measurements)
4. Late-night salivary cortisol (two measurements)

Table 4. Characteristics of screening tests in CS

<table>
<thead>
<tr>
<th>Test</th>
<th>Cutoffs</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODST</td>
<td>Negative &lt;50 nmol/L (&lt;1.8 μg/dL)</td>
<td>&gt;95%</td>
<td>80%</td>
<td>See notes below</td>
</tr>
<tr>
<td>LDDST</td>
<td>Negative &lt;50 nmol/L (&lt;1.8 μg/dL)</td>
<td>&gt;96%</td>
<td>70%</td>
<td>Useful in conditions with over-activation of HPA axis. Can be followed by CRH stimulation test.</td>
</tr>
<tr>
<td>UFC</td>
<td>Assay upper limit</td>
<td>89%</td>
<td>91%</td>
<td>False positive: elevation of serum cortisol due to physiological or pathological conditions (other than CS), high fluid intake</td>
</tr>
<tr>
<td>UFC</td>
<td>Assay upper limit</td>
<td>89%</td>
<td>91%</td>
<td>False negative: renal impairment GFR &lt;60 ml/min Check urine creatinine to verify adequacy of collection</td>
</tr>
<tr>
<td>Late night Salivary Cortisol</td>
<td>Normal (&lt;4 nmol/L, &lt;145 ng/dL)</td>
<td>92-100%</td>
<td>93-100%</td>
<td>Easily collected at home, sample can be mailed. Not suitable for night shift workers, smokers, patients with oral ulceration, critical illness or depressive illness</td>
</tr>
</tbody>
</table>
Dexamethasone tests (ODST, LDDST): can be done as an outpatient

- Hepatic enzyme inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, alcohol) lower serum dexamethasone concentration and leads to false positive results
- Oestrogens increase CBG level leading to false positive results, needs a period off (usually six weeks) oral contraceptives before testing
- Verify patient compliance of dexamethasone during test
- For paediatric patients with weight <40kg dose should be adjusted (15 μg/kg)

<table>
<thead>
<tr>
<th>Special population</th>
<th>Screening consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Use UFC&lt;br&gt;Do not use ODST/LDDST</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Use UFC, salivary cortisol or midnight serum cortisol&lt;br&gt;Do not use ODST/LDDST</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Use ODST&lt;br&gt;Do not use UFC</td>
</tr>
<tr>
<td>Adrenal incidentaloma</td>
<td>Use ODST</td>
</tr>
</tbody>
</table>

### Special investigations

#### CRH stimulation test

This test is used to differentiate Cushing disease from Pseudo-Cushing syndrome. LDDST is followed by administration of CRH (1 μg/kg, IV) 2 h after the last dose of dexamethasone. Serum cortisol and ACTH are measured 15 min later. Patients with Cushing disease should respond with an increase in ACTH and cortisol.

A cutoff of >207 nmol/L (>7.5 μg/dL) increases specificity to 87% but decreases the sensitivity.

**Uses:**

- In patients with high degree of clinical suspicion but normal UFC and negative ODST or LDDST
- Low degree of clinical suspicion but mildly elevated UFC or positive ODST or LDDST
- Patients on anti-epileptic drugs

#### Midnight serum cortisol test

This can be done on either sleeping or awake state. The patient should be admitted for a period of 48h or longer to avoid false-positive responses due to the stress of hospitalization. For a sleeping value, the blood sample must be drawn within 5-10 min of waking the patient, or through an indwelling line, to avoid false-positive results.

**Sleeping midnight serum cortisol:**

A single value of >50 nmol/L (>1.8 μg/dL) has a sensitivity of 100% for CS but low specificity.

**Awake midnight serum cortisol:**

Cutoff of >207 nmol/L (>7.5 μg/dL) has a sensitivity of 96% and specificity of 83%.

**Uses:** Easier to perform than a sleeping test but is less validated.

#### Cyclical Cushing syndrome

Suspect if the clinical features contrast with normal laboratory tests. Instruct the patient to collect a 24h urine sample or bedtime saliva when they feel symptoms have recurred. Repeat periodic testing when symptomatic.
Figure 1. Algorithm for initial evaluation of CS

Clinical suspicion of CS

Exclude exogenous glucocorticoid exposure

Perform one of the four screening tests

- **Negative test result**
  - Refer to Endocrinologist
  - Perform one other screening test

- **Positive test result**
  - Exclude physiological causes of hypercortisolism
  - Refer to Endocrinologist

- **Discrepant**
  - Suggest additional evaluation

- **Positive**
  - CS

- **Negative**
  - CS unlikely

*Where the patient has undergone a second test although the first screening test is negative because clinical probability of CS i very high.*
**Figure 2. Algorithm for diagnosing the etiology of CS**

Biochemically/clinically confirmed CS

- Plasma ACTH
  - Suppressed $< 10$ pg/mL
    - CT adrenals
    - ACTH independent disease
      - Surgery
  - Detectable $>10$ pg/mL
    - ACTH independent disease
      - MRI Pituitary
        - Lesion $>6$ mm
          - Proceed with surgery
        - Lesion $<6$ mm or No lesion
          - BIPSS
            - ACTH gradient $>2$
              - Appropriate imaging
                - + Venous sampling
                - Further evaluation

*High dose dexamethasone suppression test (HDDST): This is used to differentiate CD from ectopic ACTH. $>50\%$ suppression of plasma cortisol from the baseline value is taken as a positive response for CD. Caveat in the use of HDDST is that $90\%$ of CD shows a positive response but $10\%$ of ectopic ACTH also show a positive response. Up to $50\%$ of ectopic ACTH due to bronchial carcinoids show some suppression.*
Treatment and follow up

Treatment of CS involves a multi-disciplinary team approach including an endocrinologist, neurosurgeon, interventional radiologist and an oncologist. If the disease is left untreated, it carries high morbidity and mortality.

Figure 3. Treatment of Cushing disease (CD)

Trans sphenoidal surgery (TSS)

Remission

Monitor for recurrence

Recurrent

Repeat surgery

Radiotherapy

Recurrent/persistent disease

Bridging medical therapy

Bilateral adrenalectomy

Figure 4. Treatment of Adrenal Cushing syndrome

Adrenal Cushing syndrome

Adrenal lesion present

Adrenal adenoma bilateral/unilateral

Surgery

Adrenocortical carcinoma

Surgery

Adrenolytic therapy

Radiotherapy

Adrenal lesion absent

Further evaluation

Adrenal hyperplasia bilateral/unilateral

Further evaluation
Surgical treatment

Trans-sphenoidal surgery

The initial treatment of choice for CD is selective pituitary adenomectomy.

The resection of the tumour leads to hypocortisolism as the remaining normal corticotrophs have been suppressed due to longstanding cortisol excess. The resultant hypocortisolism, in fact provides an index of surgical success.

Peri-operative and post-operative care

Parenteral glucocorticoids must be initiated peri-operatively (parenteral hydrocortisone 100 mg one hour prior to surgery and continued 06 hourly), and should be continued on physiological doses until the HPA axis recovers (oral hydrocortisone 12-15 mg/m² (or an equivalent) as a single morning dose or divided doses with the majority given in the morning). Postoperative hypopituitarism has to be anticipated and if detected has to be adequately replaced. During the first postoperative year, the HPA axis recovers in most patients, allowing for discontinuation of glucocorticoids. HPA axis recovery can be assessed by:

- Cortisol day curve – five measurements of serum cortisol taken at 0900, 1100, 1300, 1500, and 1700 h. A mean level of 150-300 nmol/liter (5-10 μg/dl) is equivalent to a normal production rate.
- Normalization of 24-h UFC.

Assessment of remission

Assessment of remission is determined by the measurement of 9am cortisol, 48 hours following surgery. Hydrocortisone must be withheld for 12 hours prior to cortisol assessment and the patient must be monitored closely for signs of hypoadrenalism. A low postoperative 9am cortisol of <50 nmol/l is associated with remission and a low recurrence rate. UFC can also be used to assess remission. Values below 55 nmol/24 h suggest remission, whereas values in the normal range of 55-276 nmol/24 h are equivocal. However, values above the normal range indicate persistent CD.

Persistence or recurrence

Surgical success rates are low in patients harbouring macroadenomas and in patients with tumors that have invaded the dura. While a partially resected pituitary adenoma is the commonest cause for persistent hypercortisolism, other rare possibilities such as an ectopic tumour, pseudo-Cushing and McCune-Albright syndrome has to be considered. In the event of persistence or recurrence of CD, a choice of second-line therapeutic options should be discussed with the patient.

Adrenal surgery

Laparoscopic unilateral adrenalectomy is the treatment of choice in adrenal adenoma.

- As the contra lateral adrenal gland is suppressed due to inhibition of ACTH, peri operative and post-operative steroid replacement is necessary.
- Assessment of remission is done by measuring 9.00 am cortisol, 48 hours after surgery as in pituitary disease. Recovery of HPA axis can be assessed by periodic monitoring of cortisol day curves.
- Following surgery, histology should be evaluated to exclude adrenocortical carcinoma.

Medical treatment of CS

Medical treatment of CS is useful to reduce the cortisol level before definitive surgery, while awaiting the maximum efficacy of pituitary radiotherapy and in the treatment of acute, potentially life threatening complications of CS.
**Ketoconazole**

- **Dose:** starting dose 200-400mg daily up to 800 mg daily.
- **Side effects:** hepatotoxicity, hypogonadism in men.
- **Biochemical remission** – monitor blood pressure and glycaemic regulation.

**Metyrapone**

- **Dose:** 250 mg bid to 1.5 g 6 hourly.
- **Can lead to overstimulation of adrenal androgens and mineralocorticoids.**
- **Side effects:** hirsutism, acne, hypokalemia

**Mitotane**

- **Dose:** 2 g/day in divided doses up to 10g/d if tolerated.

- **Taken up by both normal and malignant adrenals. Also causes mineralocorticoid deficiency.**
- **Side effects:** adrenal crisis, GI disturbances, neurotoxicity

**Follow-up evaluation**

- **Evaluate for resolution of clinical features.**
- **Normalization of 24-h UFC.**
- **Cortisol day curve. (As mitotane increase cortisol binding globulin, markers of free plasma cortisol (24h UFC) is preferred).**

The dosage of the above drugs can be adjusted periodically according to these parameters.
Etomidate
- Dose: i.v. 0.03 - 0.3 mg/kg/h
- Fast acting and i.v. – useful for acute/life threatening CS.
- Evaluation with serial 9am cortisol levels and serum potassium.

Pituitary-directed drugs

Pasireotide
- Dose: S.C. 600 μg bid
- Side effects: hyperglycaemia
- Response has to be monitored clinically as well as with UFC and serum cortisol.

Glucocorticoid receptor antagonists

Mifepristone
- Dose: 300 – 1200 mg/day
- Can improve glycaemia and diastolic hypertension.
- Side effects – hypokalemia, endometrial hyperplasia
- Response can be monitored by clinical parameters such as weight loss, improvement of glycaemic control and diastolic blood pressure.
- Biochemical markers such as serum cortisol and UFC cannot be used to assess the response.
Annexure

**Protocol for biochemical evaluation of CS**

**Preparation:** Patients need to be off all oestrogen containing medication for six weeks prior to any measurement of serum cortisol.

**Overnight dexamethasone suppression test**

**Preparation:** performed as an outpatient.

**Protocol:** advise patient to take 1mg of dexamethasone (in children 15 μg/kg body weight) at 2300 or 0000h.

Collect serum for cortisol levels at 0800 or 0900h in the following morning.

**Low dose dexamethasone suppression test**

**Preparation:** Ensure patient is not taking any steroids or oestrogen or drugs that increase the metabolism of dexamethasone (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin).

**Protocol:** Advise the patient to take 0.5mg of dexamethasone exactly six hourly for 2 days (0900, 1500, 2100, 0300, 0900, 1500, 2100, 0300h).

Collect serum for cortisol at 0900h after ingestion of 8 doses.

**Urinary free cortisol level**

Advising the patient to collect urine for 24 hours in a plain container.

At least two measurements of urinary cortisol should be performed.

**Midnight plasma and salivary cortisol levels**

Saliva is collected between 2300 or 0000 h by passive drooling or by placing a cotton pledget in the mouth and chewing for 1-2 minutes.

The sample is stable at room temperature or refrigerator for several weeks.

At least two measurements of salivary cortisol should be performed.
High dose dexamethasone suppression test

Collect serum for a baseline 8 am cortisol measurement prior to giving dexamethasone tablets.

Advise the patient to take 2 mg dexamethasone (in children 80-120 μg/kg/day divided into four doses every 6 hours or a maximum of 2 mg every 6 hours for 2 days) every 6 hours for 2 days. (0900, 1500, 2100, 0300, 0900, 1500, 2100, 0300 h)

Collect serum for cortisol at 0800 h after ingestion of 8 doses.

Other method; advise the patient to take 8 mg dexamethasone orally at 2300 h, with measurement of an 0800 h or 0900 h cortisol level the next day.

9 am ACTH level

Collect serum for ACTH level at 0800 h or 0900 h.

Samples should be kept in an ice water bath, centrifuged, separated and frozen within a few hours.

Simultaneous plasma cortisol levels also should be measured.

References


