Cushing syndrome

Authors: Dr. Noel Somasundaram, Dr. Henry Rajaratnam, Prof. Chandrika Wijeyarathne, 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

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List of abreviations

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

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.

Table 1. Highly discriminative features of CS

Clinical feature	% of patients	Discriminative index
Easy bruising	62%	10.3
Proximal muscle weakness	56%	8
Facial plethora	94%	3
Striae (esp. reddish purple and >1 cm wide)	56%	2.5
In children : weight gain with decreasing growth velocity		

Table 2. Less discriminative clinical features of CS

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

Classification of CS

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

Table 3. Classification of CS

ACTH Dependent	ACTH Independent	Pseudo-Cushing
Cushing disease (pituitary)	Adrenal adenoma and carcinoma	Alcohol
Ectopic ACTH syndrome	Primary pigmented nodular adrenal hyperplasia and Carney syndrome	Depression
Ectopic CRH syndrome	McCune-Albright syndrome	Obesity
Macronodular adrenal hyperplasia	Aberrant receptor expression (gastric inhibitory polypeptide, interleukin -1â)	
Iatrogenic (treatment with ACTH)	Iatrogenic (steroids)	

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)

- Patients with a positive test result should be further evaluated to confirm or exclude CS.
- Patients with a negative test and low probability can be reassured. No further testing is indicated but advised to review if persistent or progressive clinical features.
- Patients with a negative test but high probability should be further evaluated to confirm or exclude CS.
- Patients with a negative test result but progressive symptoms or signs should be reevaluated periodically e.g. 6 months.

Table 4. Characteristics of screening tests in CS

Test	Cutoffs	Sensitivity	Specificity	Remarks
ODST	Negative <50 nmol/L (<1.8 µg/dL)	>95%	80%	See notes below
LDDST	Negative <50 nmol/L (<1.8 µg/dL)	>96%	70%	Useful in conditions with over-activation of HPA axis. Can be followed by CRH stimulation test.
UFC	Assay upper limit	89%	91%	False positive: elevation of serum cortisol due to physiological or pathological conditions (other than CS), high fluid intake False negative: renal impairment GFR <60 ml/min Check urine creatinine to verify adequacy of collection
Late night Salivary Cortisol Between 2300 h to 2400 h	Normal (<4 nmol/L,<145 ng/dL)	92-100%	93-100%	Easily collected at home, sample can be mailed. Not suitable for night shift workers, smokers, patients with oral ulceration, critical illness or depressive illness

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 5. Special populations and considerations

Special population	Screening consideration
Pregnancy	Use UFC Do not use ODST/LDDST
Epilepsy	Use UFC, salivary cortisol or midnight serum cortisol Do not use ODST/LDDST
Renal impairment	Use ODST Do not use UFC
Adrenal incidentaloma	Use ODST

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.

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.

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

Awake midnight serum cortisol:

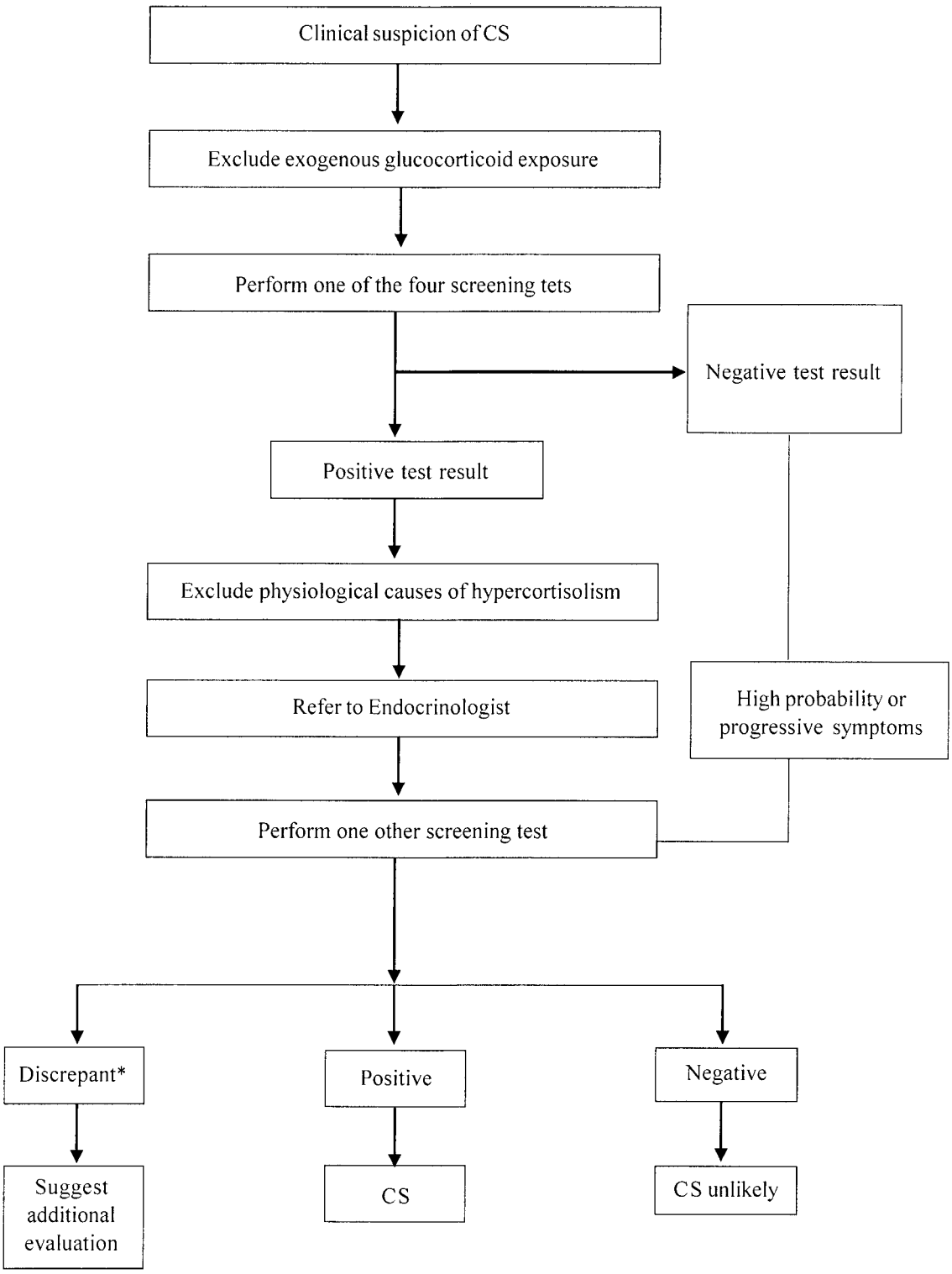
Cutoff of >207 nmol/L (>7.5 µg/dL) has a sensitivity of 96% and specificity of 83%.

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

Cyclical Cushing syndrome

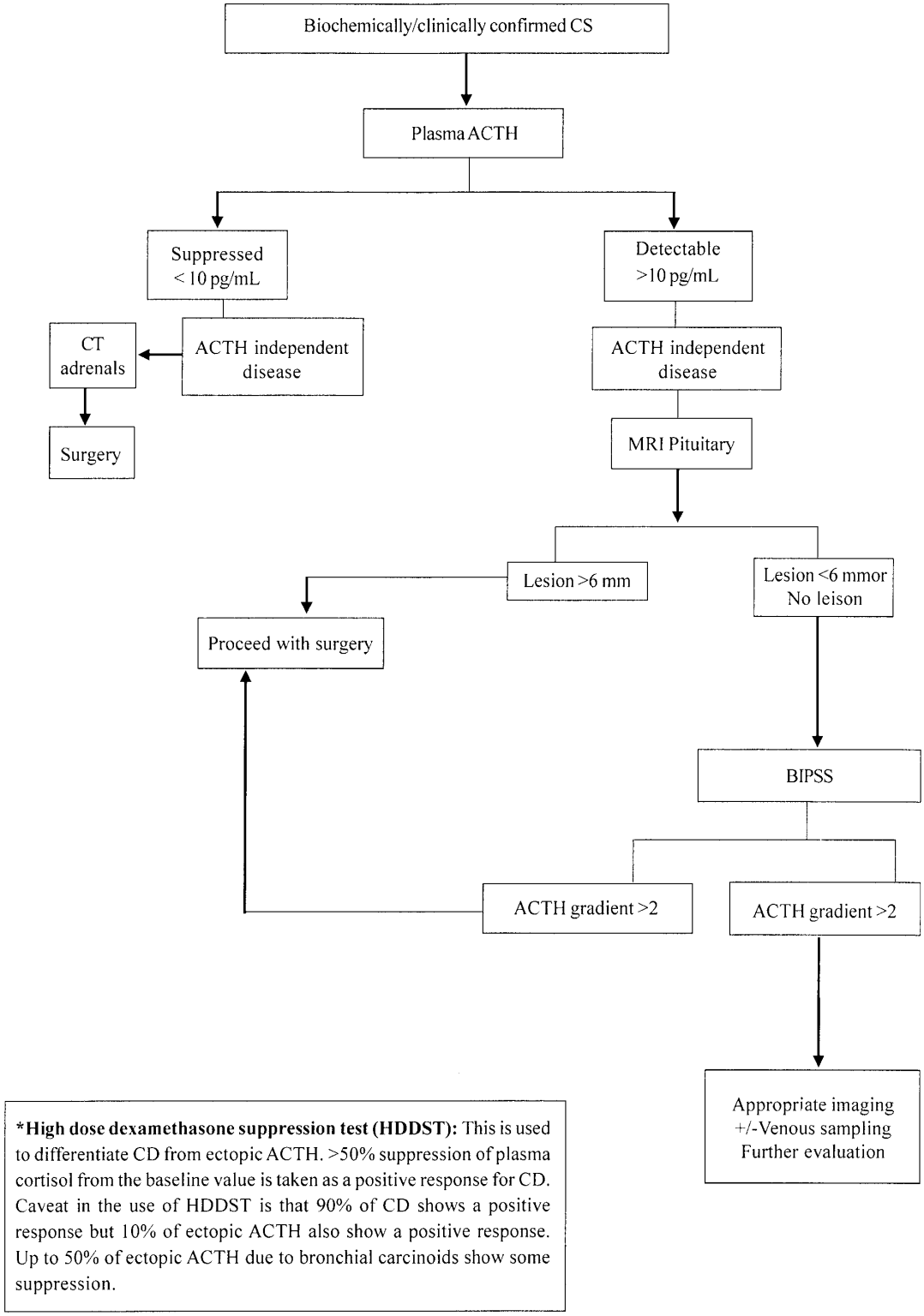
Suspect if the clinical features contrast with normal laboratory tests. Instruct the patient to collect a 24h urine sample or bedtime saliva when they feel symptoms have recurred. Repeat periodic testing when symptomatic.

Figure 1. Algorithm for initial evaluation of CS



* 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



***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)

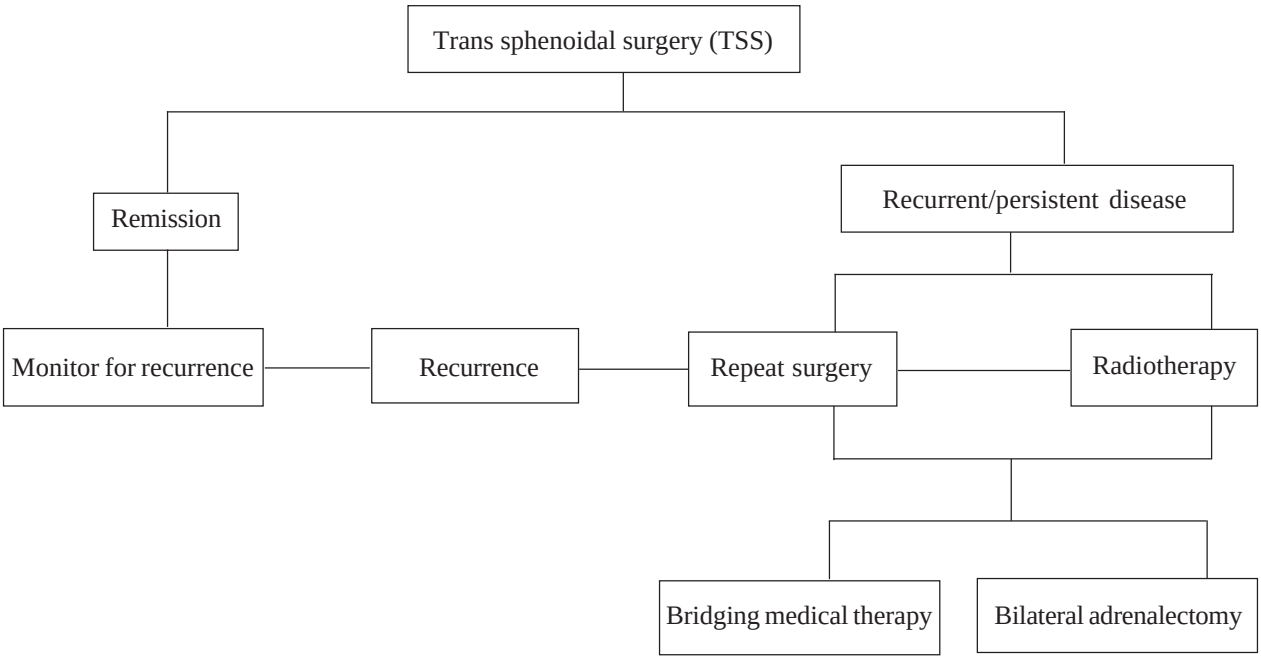
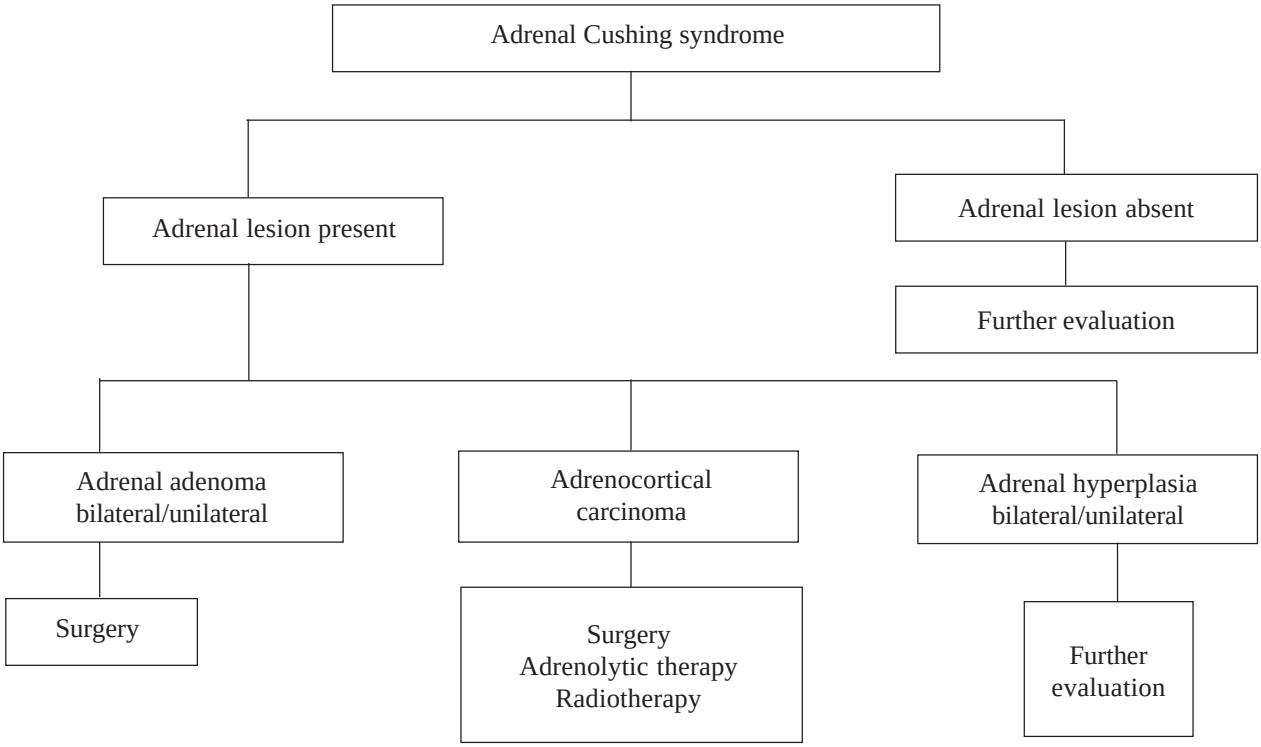


Figure 4. Treatment of Adrenal Cushing syndrome



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/m^2 (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

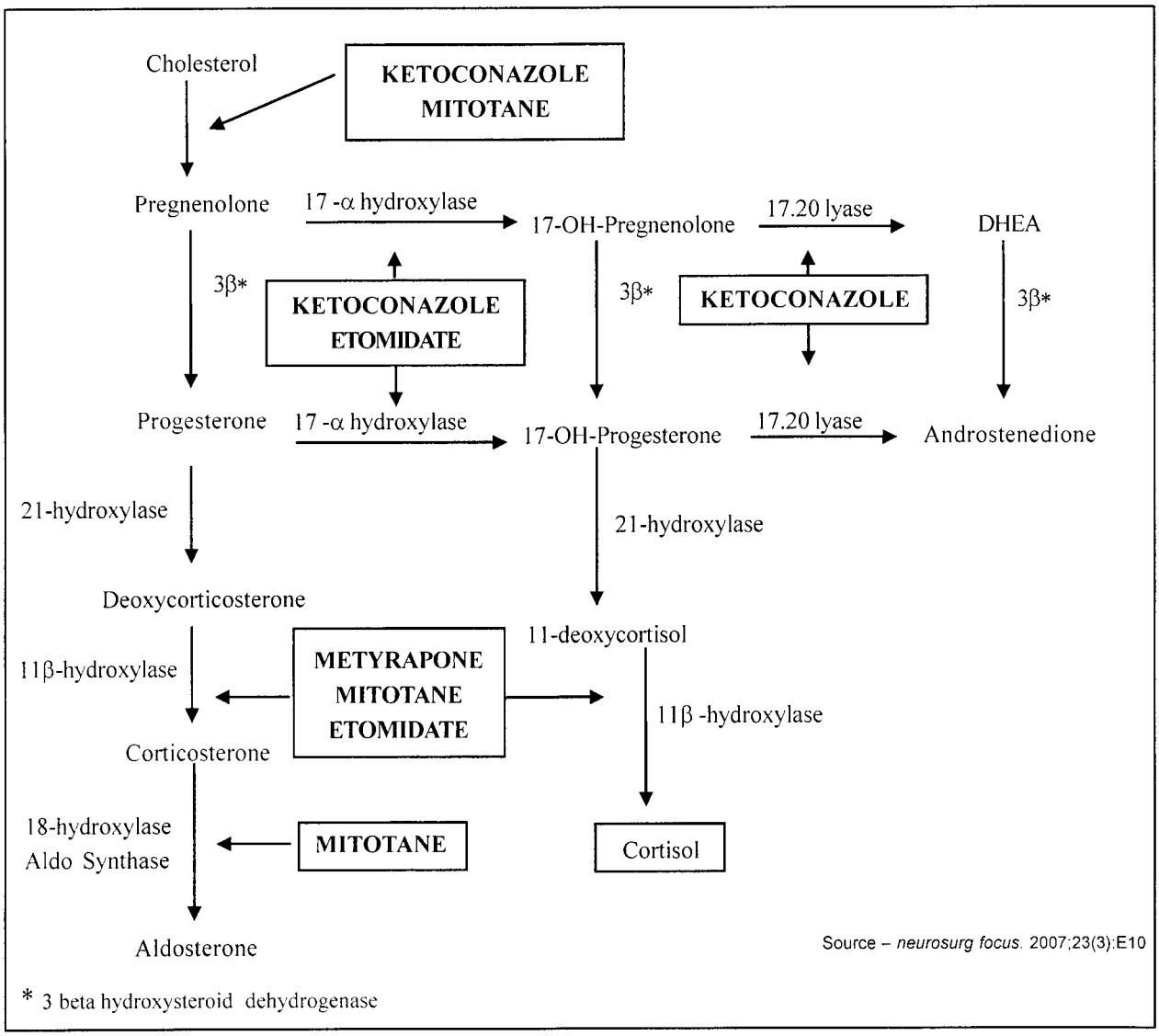
Laparoscopic unilateral adrenalectomy is the treatment of choice in adrenal adenoma.

- 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.

Figure 5. Adrenal-blocking drugs and the site of action



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, 0300 h).

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

Urinary free cortisol level

Advise 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.

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