Different aspect of Cushing syndrome from Diagnosis to Treatment

Fatemeh Rahmani.MD

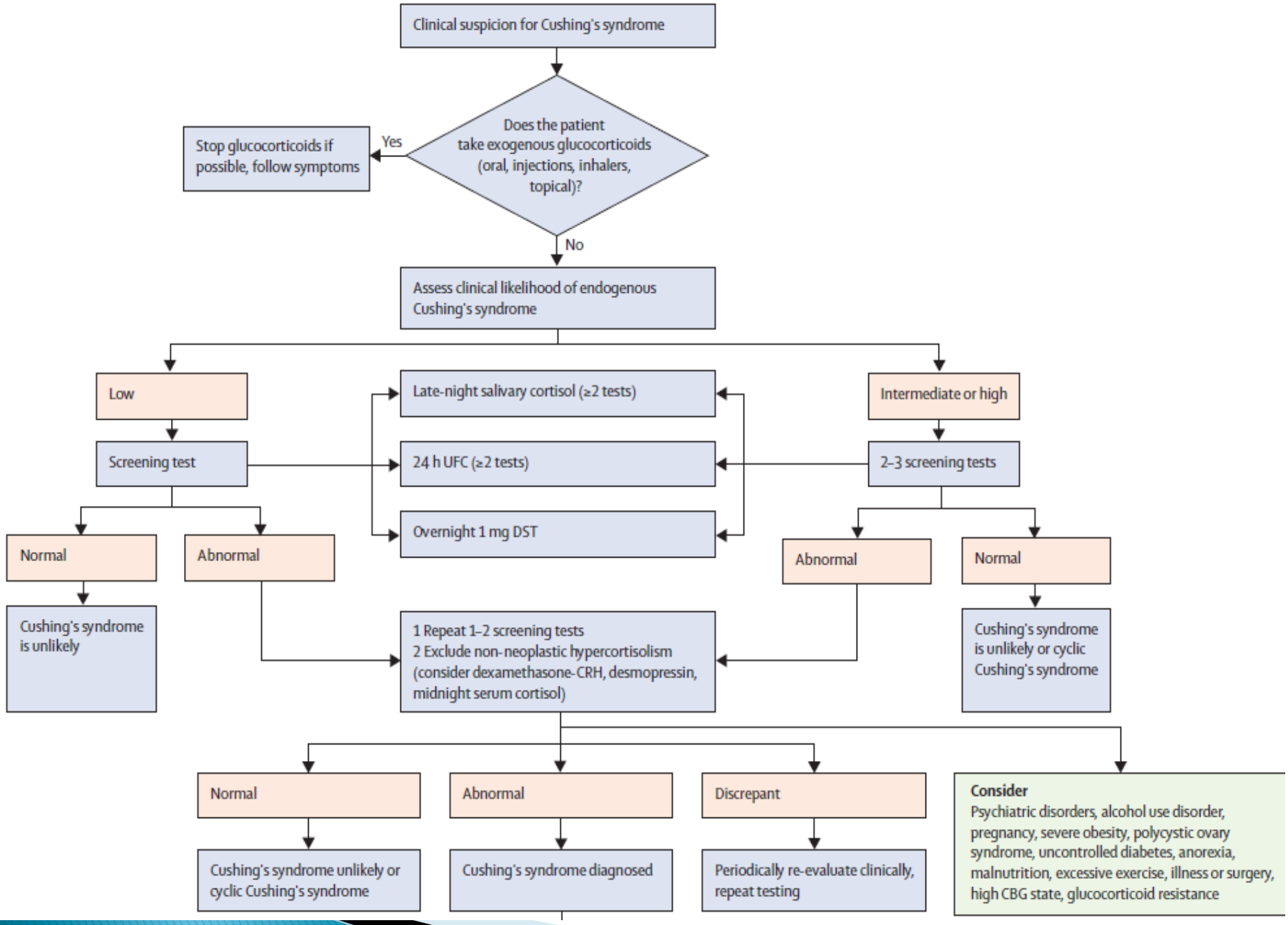
Research institute for endocrine science

Shahid Beheshti University of Medical Sciences

Agenda

- *Investigation of Patients With Suspected CS*
- *Cushing syndrome versus pseudo-Cushing*
- *Classification of Cushing syndrome*
- *Pitfalls in localization of ACTH-dependent CS*
- *Follow up after TSS*

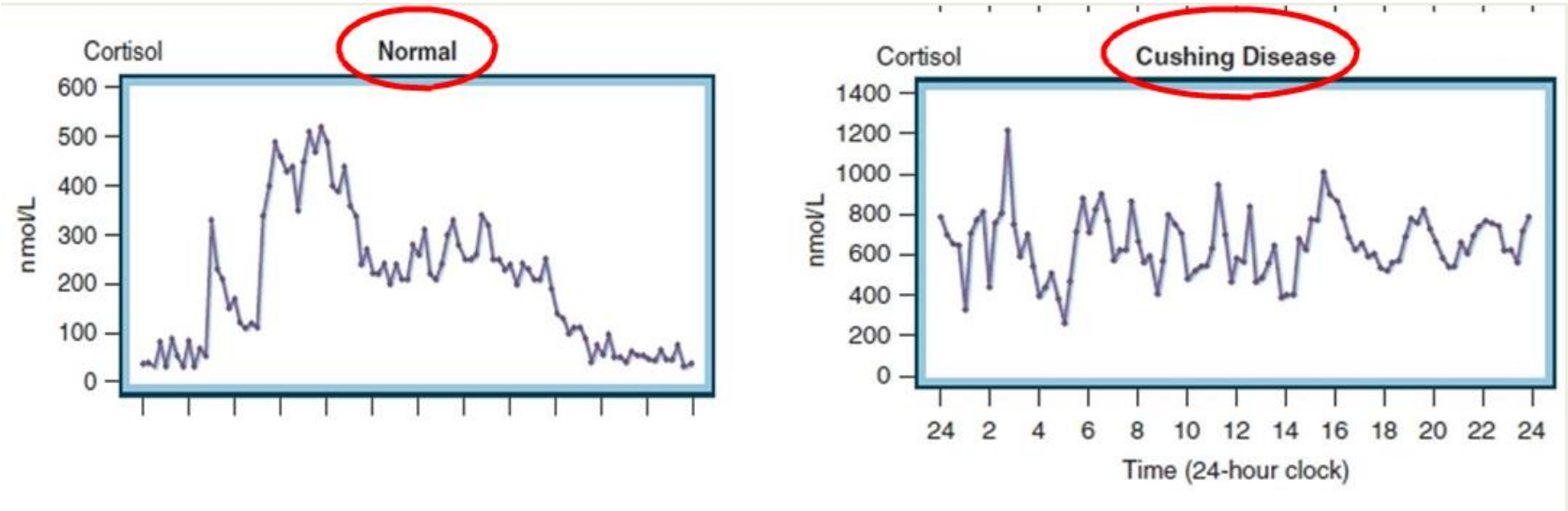
Investigation of Patients With Suspected Cushing syndrome


Clinical suspicion for Cushing's syndrome
Does the patient take exogenous glucocorticoids (oral, injections, inhalers, topical)?
Yes
Stop glucocorticoids if possible, follow symptoms
No
Assess clinical likelihood of endogenous Cushing's syndrome
Low
Intermediate or high
Screening test
2–3 screening tests
Late-night salivary cortisol (≥2 tests)
24 h UFC (≥2 tests)
Overnight 1 mg DST
Normal
Abnormal
Abnormal
Normal
Cushing's syndrome is unlikely
1 Repeat 1–2 screening tests
2 Exclude non-neoplastic hypercortisolism (consider dexamethasone-CRH, desmopressin, midnight serum cortisol)
Cushing's syndrome is unlikely or cyclic Cushing's syndrome
Normal
Abnormal
Discrepant
Consider
Psychiatric disorders, alcohol use disorder, pregnancy, severe obesity, polycystic ovary syndrome, uncontrolled diabetes, anorexia, malnutrition, excessive exercise, illness or surgery, high CBG state, glucocorticoid resistance
Cushing's syndrome unlikely or cyclic Cushing's syndrome
Cushing's syndrome diagnosed
Periodically re-evaluate clinically, repeat testing

Screening tests

- Overnight Dexamethasone Suppression Test
- Urinary Free Cortisol
- Circadian Rhythm of Plasma Cortisol
- Late night salivary Cortisol
- Low-dose Dexamethasone suppression Test

Circadian rhythm of plasma cortisol



- Ideally patients should be hospitalized for 24-48 h before test
- A midnight cortisol >7.5 μg/dL indicates CS
- A midnight cortisol <2 μg/dL, excluded CS

Late night salivary Cortisol

- Cortisole >2.0 ng/ml (5.0 nmol/L) have a 100% sensitivity and a 96% specificity for diagnosis of CS

- Avoid cigarette smoking, tobacco, steroid-containing lotion or oral gels on the day of collection

- Tends to increase with age & cardiovascular comorbid condition (HTN & DM), so the discriminating power diminishes in the elderly population

Cushing syndrome versus pseudo-Cushing

pseudo-Cushing Syndrome

- Morbid obesity
- Poorly controlled DM
- Pregnancy
- Depression and other psychiatric conditions
- Alcohol dependence

Obesity

- Simple obesity: Mildly increase in cortisol secretion rate, UFC is normal or mildly elevated

- CS screening in simple obesity is performed in the setting of poorly controlled HTN, DM, rapid progressive osteoporosis, hypokalemia

- 24-h UFC is a convenient screening test for CS in outpatient clinics

- ODST : is no longer recommended
  but suppression of plasma cortisol to <1.8 μg/dL excluded CS

Pregnancy

- HTN and DM are the most common sign of CS in pregnancy
- Pregnancy is associated with a 3-fold increase in plasma cortisol,

  UFC also rises, and dexamethasone suppression test might be fail

- Recommend the use of late night salivary cortisol and UFC
- Against using dexamethasone suppression test

- Any adrenal or pituitary adenomas should be excised

- Metyrapone, not teratogenic, effective in controlling hypercortisolism

Pseudo-Cushing syndrome

- Present with a similar clinical phenotype except
  - Cutaneous(easy bruising, thinning, friability)
  - Proximal muscle weakness

- The circadian rhythm of cortisol is preserved

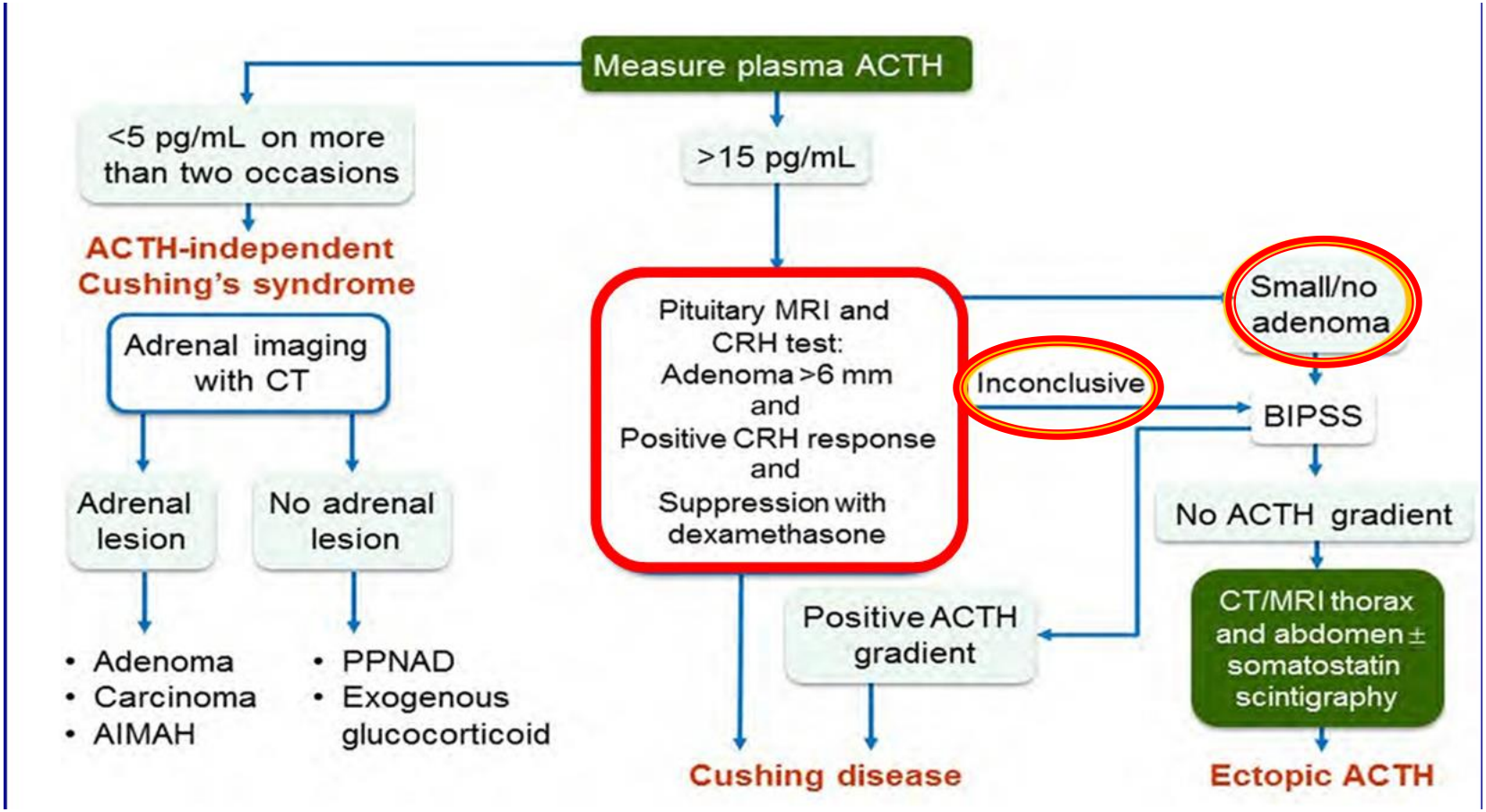
- Treatment of underlying conditions leads to resolution of symptoms

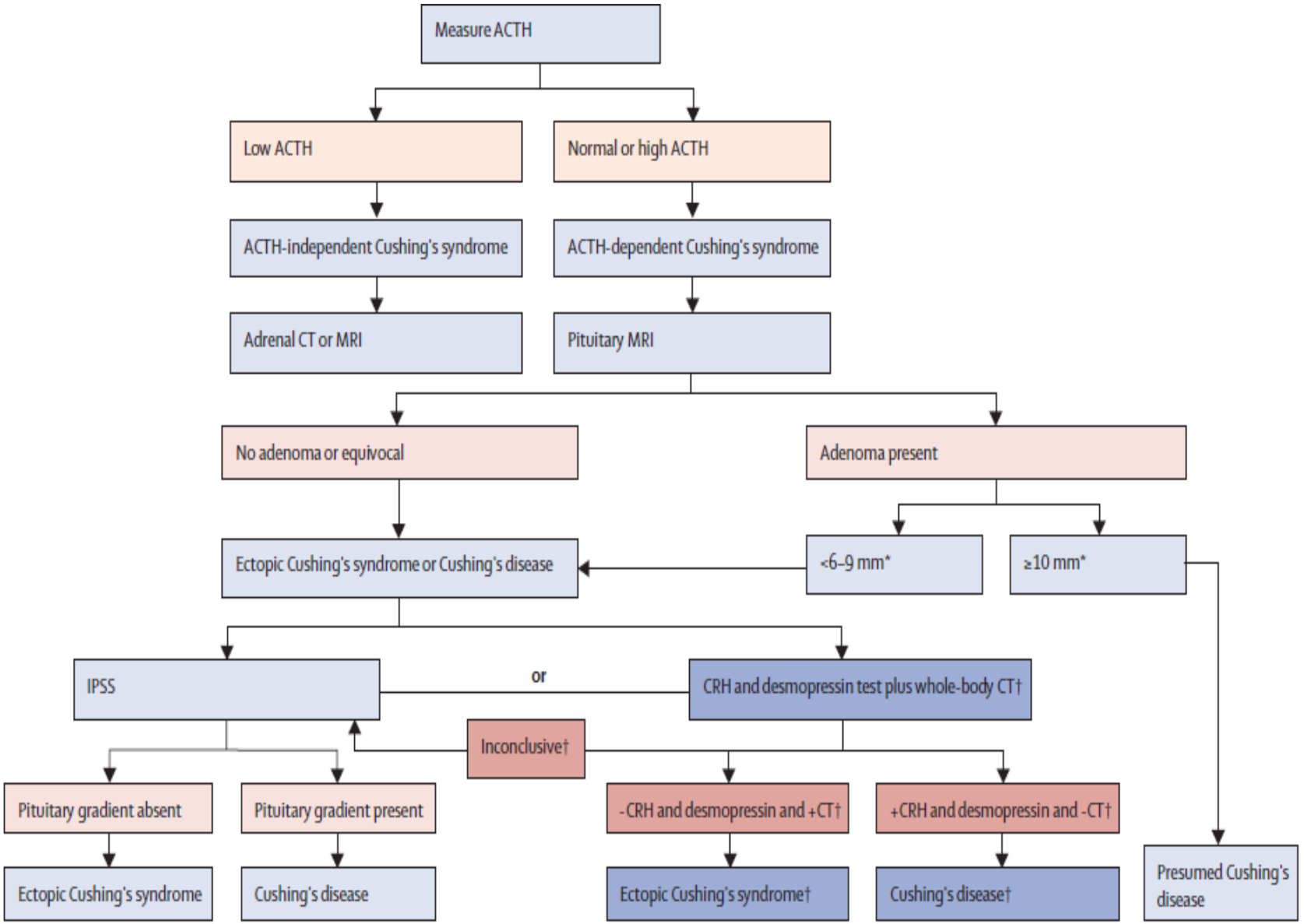
- In clinical scenario, where the test results are discordant in a patient with mild hypercortisolism, F/U is recommended for monitoring progression of symptoms and for repeat testing

Classification of Cushing syndrome

- ***ACTH –Dependent Causes***
  - Cushing disease
  - Ectopic ACTH syndrome
  - Ectopic CRH syndrome
  - Macronodular adrenal hyperplasia
  - Iatrogenic (treatment with 1-24 ACTH)

- ***ACTH –Independent Causes***
  - Adrenal adenoma and carcinoma
  - PPNAD and Carney syndrome
  - McCune-Albright syndrome
  - Iatrogenic (prednisolone, dexamethasone)


Measure plasma ACTH
<5 pg/mL on more than two occasions
ACTH-independent Cushing's syndrome
Adrenal imaging with CT
Adrenal lesion
No adrenal lesion
• Adenoma
• Carcinoma
• AIMAH
• PPNAD
• Exogenous glucocorticoid
>15 pg/mL
Pituitary MRI and CRH test:
Adenoma >6 mm
and
Positive CRH response
and
Suppression with dexamethasone
Small/no adenoma
Inconclusive
BIPSS
No ACTH gradient
CT/MRI thorax and abdomen ± somatostatin scintigraphy
Positive ACTH gradient
Cushing disease
Ectopic ACTH


Measure ACTH
Low ACTH
Normal or high ACTH
ACTH-independent Cushing's syndrome
ACTH-dependent Cushing's syndrome
Adrenal CT or MRI
Pituitary MRI
No adenoma or equivocal
Adenoma present
Ectopic Cushing's syndrome or Cushing's disease
<6–9 mm*
≥10 mm*
IPSS
or
CRH and desmopressin test plus whole-body CT†
Inconclusive†
Pituitary gradient absent
Pituitary gradient present
-CRH and desmopressin and +CT†
+CRH and desmopressin and -CT†
Ectopic Cushing's syndrome
Cushing's disease
Ectopic Cushing's syndrome†
Cushing's disease†
Presumed Cushing's disease

Pitfalls in differential diagnosis of ACTH-dependent CS

Pitfalls in differential diagnosis of ACTH-dependent CS

- Severe CD Mimicking Classic Ectopic ACTH Syndrome
- Mild Ectopic ACTH Syndrome Mimicking Classic CD

Ectopic ACTH Syndrome

- Rapid progression
- Weight loss
- More hyperpigmentation
- more substantial hypokalemia
- Greater degree of ACTH
- Greater degree of cortisol hypersecretion and UFC
- weaker cortisol suppression after HDDST

Noninvasive biochemical testing

1)HDDST

- Up to 50% of patients with CD may fail to response to HDDST
- About 10% of patients with EAS show suppression of cortisol

50% (usually bronchial carcinoids)

2)CRH stimulation test

- A response to CRH differentiate CD from other causes of CS
- Up to15% of patients with CD may be misdiagnosed by the test

3)Desmopressin stimulation test

- Desmopressin, stimulates ACTH release in most patients with CD and usually induces a response similar to that of CRH
- up to 20 % of those with CD do not respond to this test

4)Combination testing with CRH /desmopressin and HDDST

- If the two tests (CRH and/or desmopressin, and HDDST) both indicate CD, rare patients with ectopic ACTH secretion are falsely diagnosed, but a number with CD are missed

5) Pituitary MRI

- A sensitivity of 80%
- Unable to find lesions in pituitary gland in 30-50% of CD patients
- Pituitary incidentaloma <6 mm are seen in 10-20% of the normal population

6)Bilateral inferior petrosal sinus sampling

- Gold standard for DDX of pituitary or ectopic hypercortisolism
- Sensitivity of 88-100% , specificity of 67-100%
- Since ACTH secretion is intermittent, using CRH/Desmopressin increase the study's sensitivity

Indications of BIPSS

- ACTH-dependent CS biochemically and NL pit MRI (no lesion, or a lesion < 6 mm)
- In cases without respond to hormone tests
- discrepancy between the biochemical and imaginal findings
- In post-hypophysectomy patients with persistent CS

Limitation of BIPSS

- Invasive procedure
- Limited availability
- Rate of success depends on experience neuroradiological team

- False-positive:
  rarely in ectopic CRH syndrome
  adrenal tumor that pituitary ACTH is incompletely suppressed

- False-negatives :
  Poor catheter placement
  Anomalous or asymmetric venous drainage
  little initial experience
  tumors with cyclical ACTH secretion without respond to Desmo

Treatment of CD postoperatively follow up

Surgical Treatment

Cushing Disease

- TSS: Remision rate in microadenoma is 70% -90%
  in macroadenoma is 50%
- Bilateral adrenalectomy (Nelson syndrome)

Ectopic ACTH Syndrome

- Resection of tumor
- Bilateral adrenalectomy and monitoring

Radiotherapy

- Is not recommended as a primary treatment except:

  - patients not responding to pituitary microsurgery
  - who have undergone bilateral adrenalectomy
  - patients with established Nelson disease

Follow up after TSS

•perioperative and postoperative glucocorticoid covering is advised

•On days 2 to 5 postoperatively, a 9 AM plasma cortisol level should be measured with the patient having omitted glucocorticoid for 24-h

•Remission is generally defined as morning serum cortisol <5 μg/dL or UFC <10–20 μg/d postoperatively

• hypocortisolemic patients receive glucocorticoid replacement and education about adrenal insufficiency after surgical remission

Follow up after TSS

•Re-evaluating other pituitary hormone deficiencies (serum Na ,free T4, prolactin)in the post operative period is recommended

• evaluate patients for possible CD recurrence when the HPA axis recovers, then annually, or sooner if clinical symptoms are present

• LNSC is more sensitive than UFC and DST for CD recurrence

•A postoperative pituitary MRI within 1–3 months after TSS is recommended

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TAKE HOME MESSAGE

- Differentiate CS from pseudo-Cushing with medical history, clinical examination, and biochemical test
- Radiological investigation should be avoided before proven CS
- Attention to pitfalls in localization of ACTH-dependent CS
- Close observation of patient with Cushing disease after TSS

Thank you for your attention