Approach to the Patient: Diagnosis of Cushing Syndrome ; pitfalls

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Approach to the Patient

Approach to the Patient: Diagnosis of Cushing Syndrome

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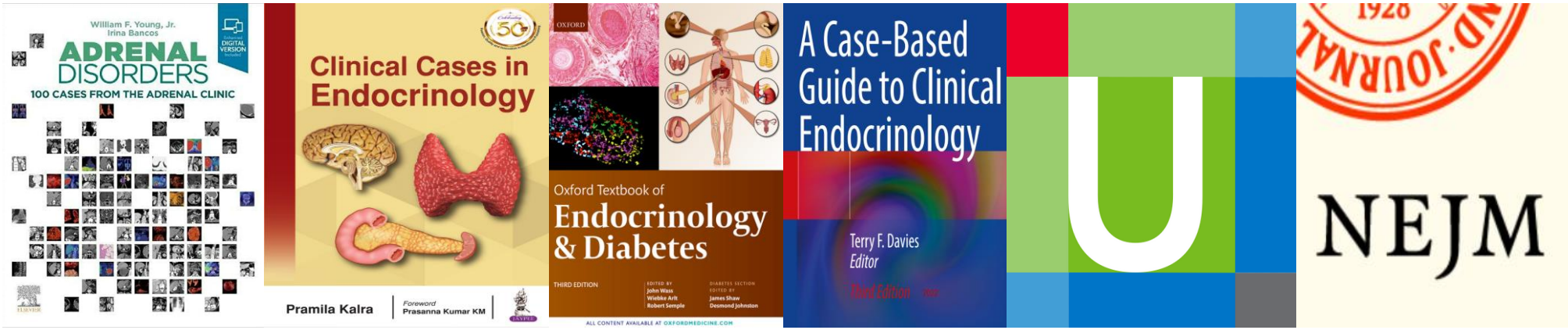


agenda

- When to Screen
- Who should we screen
- How to Screen
- How to differentiate the different causes
- The latest developments in biochemical and imaging techniques

Case 1

- A 45 y/o woman was referred to the University Medical Center from another hospital for possible Cushing syndrome
- weight gain of 6 kg in 18 months
- central obesity
- moderate muscle weakness
- Insomnia
- Hypertension had been diagnosed 3 years ago and was treated with nifedipine 30 mg.

Case1

- She consulted a psychiatrist for 14 months because of depressive complaints and there was suspicion of bipolar disorder. For this, she is treated with carbamazepine 200 mg twice daily.
- There is no alcohol or drug abuse.

Drug hx :

- nifedipine 30 mg
- carbamazepine 200 mg twice daily

At physical examination

- BMI of 28 kg/m2
- BP of 150/95 mmHg was measured.
- The patient had a moderate plethoric facial appearance
- supraclavicular fat pads
- some central obesity without striae.
- minimal muscle atrophy of the upper legs, and no ecchymoses, hirsutism, or edema was observed

Lab data

- UFC was found of 2 times the upper limit of normal (ULN)
- 1-mg dexamethasone suppression test (DST) with a cortisol value of 5.62 µg/dL
- a high normal ACTH level of 40.9 pg/mL (ULN 50 pg/mL)
- Pituitary imaging with magnetic resonance imaging (MRI) showed a small cystic lesion at the left side of the pituitary

Cushing syndrome ; Why it is so hard

The most difficult questions

1)Does the patient have CS ? And ACTH dependent or independent?

2)In ACTH dependent disease is it pituitary or ectopic?

3)If it is ectopic, where is it ?

4)Unlike other endocrine disorders ; there is no single test you need to build a wall of evidence ?

Cushing syndrome

- CS results from **prolonged exposure to excess glucocorticoids**, either from exogenous glucocorticoids or an endogenous source
- The **most common cause : iatrogenic**, resulting from exogenous pharmacologic doses of corticosteroids.
- Endogenous CS → ACTH-dependent (80 to 85% of cases)
  → ACTH-independent (15 to 20%)

incidence of endogenous CS is 0.2 to 5.0 per million people per year

prevalence is 39 to 79 per million in various populations

Cushing syndrome

- severe disease
- long-lasting effects
- low quality of life

- Hypercortisolism
  - cardiovascular events (MI 4.5 times higher)
  - cerebrovascular events (stroke)
  - sepsis
  - thromboembolism with 3.5 to 5 times increased mortality risk

Exogenous Steroids

- **similar symptoms** as seen in endogenous CS.
- **Glucocorticoid use is most prevalent cause** of CS.
- profuse prescription and over-the-counter : **drug history in the initial approach**
- pharmacokinetic , pharmacodynamic properties ; duration; route › net systemic effect
- urinary or blood mass spectrometry assays
- important to screen for **concomitant use of other drugs** such as **antifungals**, **protease inhibitors**, or **estrogens.**

Exogenous Steroids

- **Dose-related pattern:**

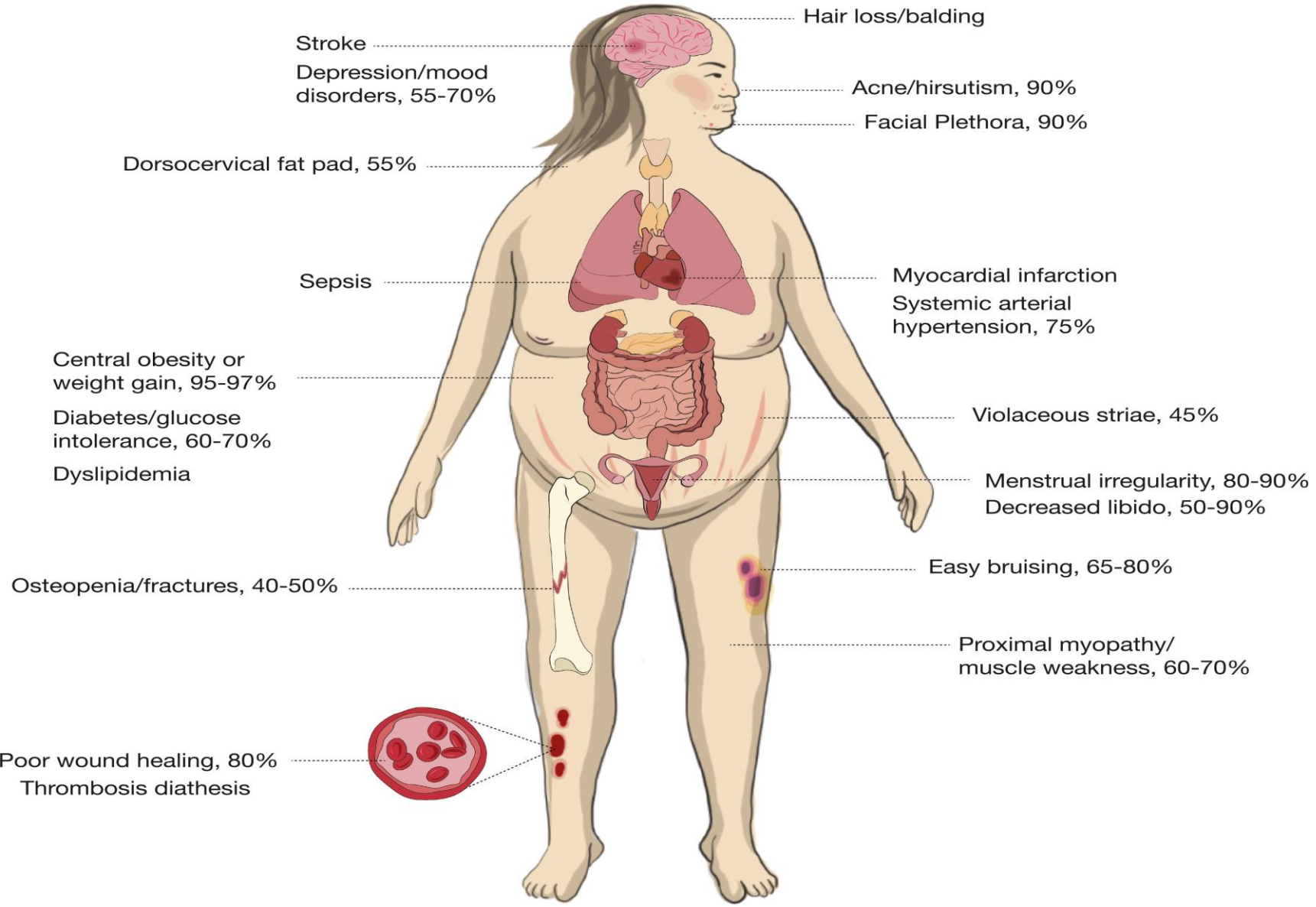
epistaxis and weight gain → prednisone equivalent dose of > 5 to 7.5 mg/d

depression and high blood pressure → > 7.5 mg/d

Exogenous Steroids

- **Consider administration forms other than the oral types**
- adrenal insufficiency in corticosteroid users of intra-articular injection is similar (52% absolute risk) to oral corticosteroids (48.7%)
- locally applied corticosteroids such as nasal (4.2%), dermal (4.7%), and inhaled (7.8%) are significantly associated with adrenal insufficiency
- Combination of different administration routes increased risk of adrenal insufficiency even up to 42.7%

Clinical features



SPECIAL FEATURE

Clinical Practice Guideline

The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, John Newell-Price, Martin O. Savage, Paul M. Stewart, and Victor M. Montori

TABLE 1. Overlapping conditions and clinical features of Cushing's syndrome[a]

Symptoms	Signs
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity	
	Easy bruising
	Facial plethora
	Proximal myopathy (or proximal muscle weakness)
	Striae (especially if reddish purple and > 1 cm wide)
	In children, weight gain with decreasing growth velocity
Cushing's syndrome features in the general population that are common and/or less discriminatory	
Depression	Dorsocervical fat pad ("buffalo hump")
Fatigue	Facial fullness
Weight gain	Obesity
Back pain	Supraclavicular fullness
Changes in appetite	Thin skin[b]
Decreased concentration	Peripheral edema
Decreased libido	Acne
Impaired memory (especially short term)	Hirsutism or female balding
Insomnia	Poor skin healing
Irritability	
Menstrual abnormalities	
In children, slow growth	In children, abnormal genital virilization
	In children, short stature
	In children, pseudoprecocious puberty or delayed puberty

Signs/symptoms of Cushing syndrome	Prevalence (%)
(Abdominal) obesity/weight gain	75-95
Rounded face (moon face)	81-90
Supraclavicular/dorsocervical fat pad (buffalo hump)	50
Hirsutism/alopecia	75
Facial plethora	**70-90**
Violaceous striae	**44-50**
Acne	20-35
Easy bruising	**35-65**
Menstrual irregularity	70-80
Decreased libido	24-80
Neuropsychiatric (emotional lability/depression, psychosis/mania, cognitive dysfunction)	70-85
Muscle weakness/atrophy	**60-82**
Osteopenia/fractures	40-70

Symptom	Prevalence in Cushing's syndrome*	Prevalence in the general population
Nephrolithiasis	20–50%	1–20% (dependent on country) (41)
Thin skin	37%	Unclear
Lack of vitamin D	Unclear, but at least as frequent as in the general population	40–100% (42)
Edema	Unclear	Dependent on disease
Decreased growth in children	70–80%	3%
Asymptomatic urinary tract infections	Unclear	Very common (43)
Sleeping disorder, fatigue	60%	Up to 25% (44)
Easy bruising	35–65%	Unclear
Decreased libido	24–80%	29% (women) (45)
Poor wound healing	Unclear	Unclear
Menstrual changes (women)	70–80%	Dependent on illness
Hair loss	31%	Up to 65% (46)

Why it is so hard
When to Screen

- The clinical presentation of CS can be variable , depending on a patient's **age**, **sex**, **severity**, and **duration** of cortisol excess.

- Patients often present with **nonspecific features** such as (abdominal) obesity , rounded face, menstrual irregularity, and depression; **gradually develop** over time and emerge **sequentially**

- pseudo-Cushing states: **severe obesity**, **alcoholism**, **PCOS**, and **neuropsychiatric disorders**, are beyond more prevalent

Who should we screen

- 1. Patients with adrenal incidentalomas (adenoma).
- 2. Patients who show Cushingoid-related features which are uncommon for age (HTN, osteoporosis, or female balding).
- 3. Multiple symptoms, or progressive over time, in particular when specific cushingoid features are present.
- 4. Children with a combination of increasing weight and decreasing height percentile.

When to Screen …pitfalls

- patients with difficult to treat diabetes or hypertension
- In case of pituitary incidentaloma, routine screening for ACTH-hypersecretion is not recommended.
- screening for hypercortisolism in asymptomatic persons is useful for detecting preclinical Cushing disease?????
- screening for hypercortisolism may be considered in patients with unexplained venous thrombotic events

the first-line screening tests

- Overnight 1mg DST
- 24 hours UFC
- Late night salivary cortisol test (LNSC)
- 48 2mg/day DST
- Scalp hair analysis (hair cortisol and cortisone)
- Diurnal serum cortisol
- Old photographs

There is no specific order of screening, but the choice test can be made based on individual patient characteristics

second-line screening tests

- midnight serum cortisol
- combined low dose dexamethasone ST -CRH test
- DDAVP stimulation test
- Intravenous DST
- High dose DST overnight 8 mg
- High dose DST two day 8mg/d

In the patient with obvious and severe CS don,t waste time for tests

Screening tests

- ***Sensitivity***
- ***Specificity***
- ***Likelihood ratios***
- ***ROC (Receiver Operating Characteristic) curve and area***

Availability
Cost
Acceptability
Accuracy
Reproducibility
Noninvasive

Likelihood ratio

- Likelihood ratio =the likelihood of a test result in patients *with* the disease / the likelihood of a test result in patients *without* the disease

$$LR+ = \frac{\text{probability that test is positive in diseased people}}{\text{probability that test is positive in nondiseased people}} = \frac{TPR}{FPR}$$

Sens/ 1_spe

$$LR- = \frac{\text{probability that test is negative in diseased people}}{\text{probability that test is negative in nondiseased people}} = \frac{FNR}{TNR}$$

1_sens/ spec

Likelihood ratio

- LR(+) = sensitivity/(1-specificity)
- LR(-) = (1-sensitivity)/specificity

Likelihood Ratios

- Allow many levels of interpretation for a "positive" test

LR	Meaning
>10	**Strong evidence to rule in a disease**
5-10	Moderate evidence to rule in
0.5-2	Indeterminate
0.2-0.5	Weak evidence to rule out
0.1-0.2	Moderate evidence to rule out
<0.1	**Strong evidence to rule-out disease**

Sensitivity and Specificity of tests in Cushing

Diagnostic test	LR positive test (95% CI)	LR negative test (95% CI)	Diagnostic OR (95% CI)[a]	I^2 (%)
Individual tests (n = no. of studies)				
UFC (n = 14)				
Pooled results	10.6 (5.5–20.5)	0.16 (0.08–0.33)	95.4 (37.8–240.3)	44
Midnight serum cortisol (n = 6)				
Pooled results	9.5 (1.7–54.1)	0.09 (0.03–0.28)	122.1 (15.3–974.6)	78
Assay driven (n = 2)	1.8 (0.5–6.9)	0.47 (0.23–0.96)	6.47 (1.6–26.6)	0
Outcome driven (n = 4)	26.6 (0.9–768.5)	0.05 (0.03–0.08)	581.11 (155.7–2169.5)	0[a]
Midnight salivary cortisol (n = 4)				
Pooled results	8.8 (3.5–21.8)	0.07 (0.00–1.20)	165.4 (26.9–1015.0)	50
1-mg overnight DST (n = 14)				
Pooled results	11.6 (5.8–23.1)	0.09 (0.05–0.14)	146.6 (67.8–316.9)	11
<50% had CS (n = 11)	16.4 (9.3–28.8)	0.06 (0.03–0.14)	328.7 (125.9–857.9)	0
>50% had CS (n = 3)	2.8 (1.3–6.3)	0.11 (0.06–0.19)	48.1 (16.9–136.3)	0[b]
2-day 2 mg DST (n = 8)				
Pooled results	7.3 (3.6–15.2)	0.18 (0.06–0.52)	51.6 (20.0–133.3)	0
Test combinations[c]				
UFC + 1-mg overnight DST (n = 3)				
Pooled results	15.4 (0.7–358.0)	0.11 (0.007–1.57)	149.4 (1.3–16811.5)	90
UFC + Midnight serum cortisol (n = 1)				
Pooled results	73.0 (29.1–183.2)	0.02 (0.001–0.34)	3315 (173–63513)	NA
UFC + 1-mg overnight DST + midnight serum cortisol (n = 1)				
Pooled results	174.1 (11.0–2764.2)	0.02 (0.001–0.34)	7965 (153.8–412492)	NA

CI, Confidence interval; LR, Likelihood ratio; NA, incalculable for less than three studies; OR, odds ratio.

[a] Subgroup-interaction test, $P = 0.000005$.

[b] Subgroup-interaction test, $P = 0.0008$.

[c] Judged positive when all included tests were positive.

	Approximate change in probability (%)
Likelihood ratios between 0 and 1 reduce the probability of disease	
0·1	−45
0·2	−30
0·3	−25
0·4	−20
0·5	−15
1·0	0
Likelihood ratios greater than 1 increase the probability of disease	
2	+15
3	+20
4	+25
5	+30
6	+35
7	
8	+40
9	
10	+45

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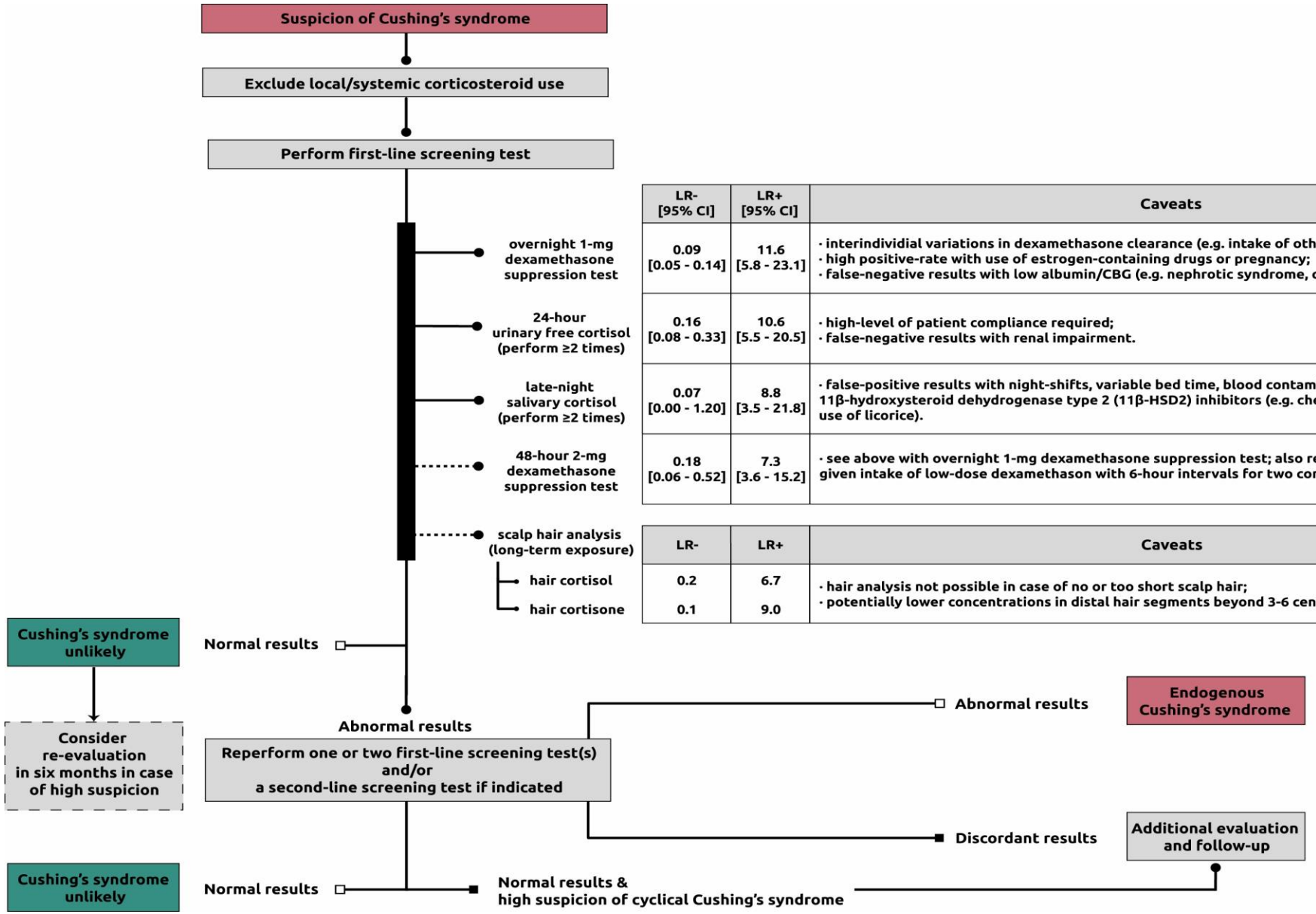
***Table 3*: Likelihood ratios and bedside estimates**



	LR- [95% CI]	LR+ [95% CI]	Caveats
overnight 1-mg dexamethasone suppression test	0.09 [0.05 - 0.14]	11.6 [5.8 - 23.1]	· interindividial variations in dexamethasone clearance (e.g. intake of other drugs, alcohol, liver/renal failure); · high positive-rate with use of estrogen-containing drugs or pregnancy; · false-negative results with low albumin/CBG (e.g. nephrotic syndrome, critical illness, malnutrition).
24-hour urinary free cortisol (perform ≥2 times)	0.16 [0.08 - 0.33]	10.6 [5.5 - 20.5]	· high-level of patient compliance required; · false-negative results with renal impairment.
late-night salivary cortisol (perform ≥2 times)	0.07 [0.00 - 1.20]	8.8 [3.5 - 21.8]	· false-positive results with night-shifts, variable bed time, blood contamination or use of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inhibitors (e.g. chewing or smoking tobacco, use of licorice).
48-hour 2-mg dexamethasone suppression test	0.18 [0.06 - 0.52]	7.3 [3.6 - 15.2]	· see above with overnight 1-mg dexamethasone suppression test; also requires more patient compliance given intake of low-dose dexamethason with 6-hour intervals for two consecutive days.

	LR-	LR+	Caveats
hair cortisol	0.2	6.7	· hair analysis not possible in case of no or too short scalp hair; · potentially lower concentrations in distal hair segments beyond 3-6 centimeter.
hair cortisone	0.1	9.0	

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	LR-	LR+	Caveats
scalp hair analysis (long-term exposure)			
hair cortisol	0.2	6.7	· hair analysis not possible in case of no or too short scalp hair; · potentially lower concentrations in distal hair segments beyond 3-6 centimeter.
hair cortisone	0.1	9.0	

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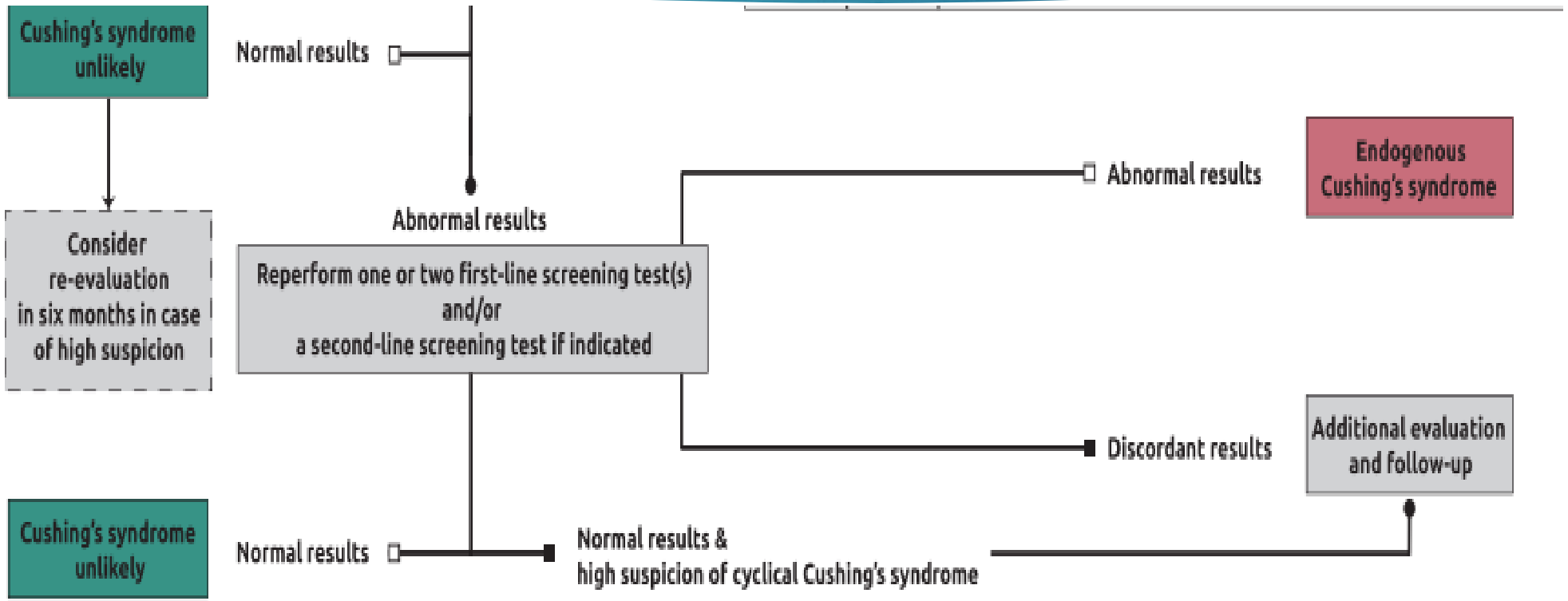

Cushing's syndrome unlikely
Normal results
Abnormal results
Consider re-evaluation in six months in case of high suspicion
Reperform one or two first-line screening test(s) and/or a second-line screening test if indicated
Abnormal results
Endogenous Cushing's syndrome
Discordant results
Additional evaluation and follow-up
Cushing's syndrome unlikely
Normal results
Normal results & high suspicion of cyclical Cushing's syndrome

- Patients should be subsequently tested again with 1 or 2 first-line screening tests or a second-line screening test.
- second-line screening test :
  - combined dexamethasone-CRH test
  - midnight serum cortisol
  - DDAVP stimulation test

Endogenous CS is unlikely with 2 normal test results and requires no further evaluation unless a cyclical CS or a (rare) glucocorticoid hypersensitivity is suspected.

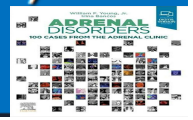
24-hour urinary cortisol excretion
False positive

- Physiologic hypercortisolism (pseudo-Cushing's)
  - severe depression
  - PCOS
- High fluid intake : urine volumes of more than 3 liters

UpToDate.

False + with:

ETOHism
Depression
Anorexia nervosa
Severe illness (eg, ICU)
Carbamazepine (HPLC assays)
High urine volume (eg, > 4L)
> 24-hr collection



Late-night salivary cortisol

- IT is based on the fact that the normal nadir in serum cortisol is preserved in obese and depressed patients but not in those with CS.
- LNSC measurement is not a good test for patients with erratic sleep schedules or shift work
- older men some with co-morbidities of diabetes and/or hypertension, showed poor specificity.
- perhaps age-specific normative values must be used for its interpretation.

Late-night salivary cortisol false positive

Use of substances containing glycyrrhizic acid (11βHSD2 inhibitor):

- licorice candies
- some teas
- Carbenoxolone
- Gossypol
- Phthalates

LNSC>1000ng/dl is contamination

- For collecting saliva: 30 mints before collection not to drink ; eat ; brush their teeth; smoking.
- and steroid cream for 24 hours before collection

1-mg DST false positive

- DX is metabolized primarily by hepatic CYP3A4 and therefore enzyme inducing drug enhance dexamethasone clearance:
  - carbamazepine
  - Phenytoin
  - Phenobarbital
  - Rifampin
  - Pioglitazone
- fast dexamethasone metabolism ;
- mistake timing of dexa ingestion or forgut it
- Consume oral estrogen preparations (increased in CBG)

Pseudo-CS

- Endogenous hypercortisolism nonneoplastic or physiologic hypercortisolism
- a phenomenon that can occur in many medical disorders such as
  - chronic alcoholism,
  - chronic kidney disease
  - type 2 DM
  - psychiatric conditions.

- Hypercortisolism in these conditions is mainly mediated by :
  - activation of the HPA axis
  - decreased sensitivity to glucocorticoid negative feedback

Which test is suitable for Pseudo-CS

- the first-line tests show normal **LNSC** and suppression of cortisol with **DST**

- If there is diagnostic uncertainty, a 2 days Low dose DST (2 mg/d) or secondary tests can be performed, including **DDAVP stimulation**, and **dexamethasone-CRH testing**.

New Developments: Potential of Hair Cortisol Measurement as a Diagnostic Tool

- A relatively novel method
- scalp hair analysis
- a patient friendly and noninvasive method
- long-term cortisol exposure of the past months
- This method enables retrospective assessment of both cortisol and its inactive variant cortisone are incorporated in hair.

- The routine first-line screening tests capture cortisol exposure for up to several days, whereas **hair analysis** allows assessment of glucocorticoid concentrations in the **past months to years**.

- Depending on the length of the collected hair sample, it is possible to make timelines of past glucocorticoid exposure ;(growth rate of scalp hair is 1 cm/mo.)
  - to capture episodes of hypercortisolism
  - to approximate the beginning and course over time of hypercortisolism.

- In these studies, a 3-cm hair sample per patient was used (corresponding to mean glucocorticoid levels of roughly past 3 months) and hair analysis was performed with either immunoassay or liquid chromatography tandem mass spectrometry.

LR+8.7
LR_0.14

- Hair cortisone (sensitivity 87%, specificity 90%)

- hair cortisol (sensitivity 81%, specificity 88%)

LR+6.7
LR_0.2

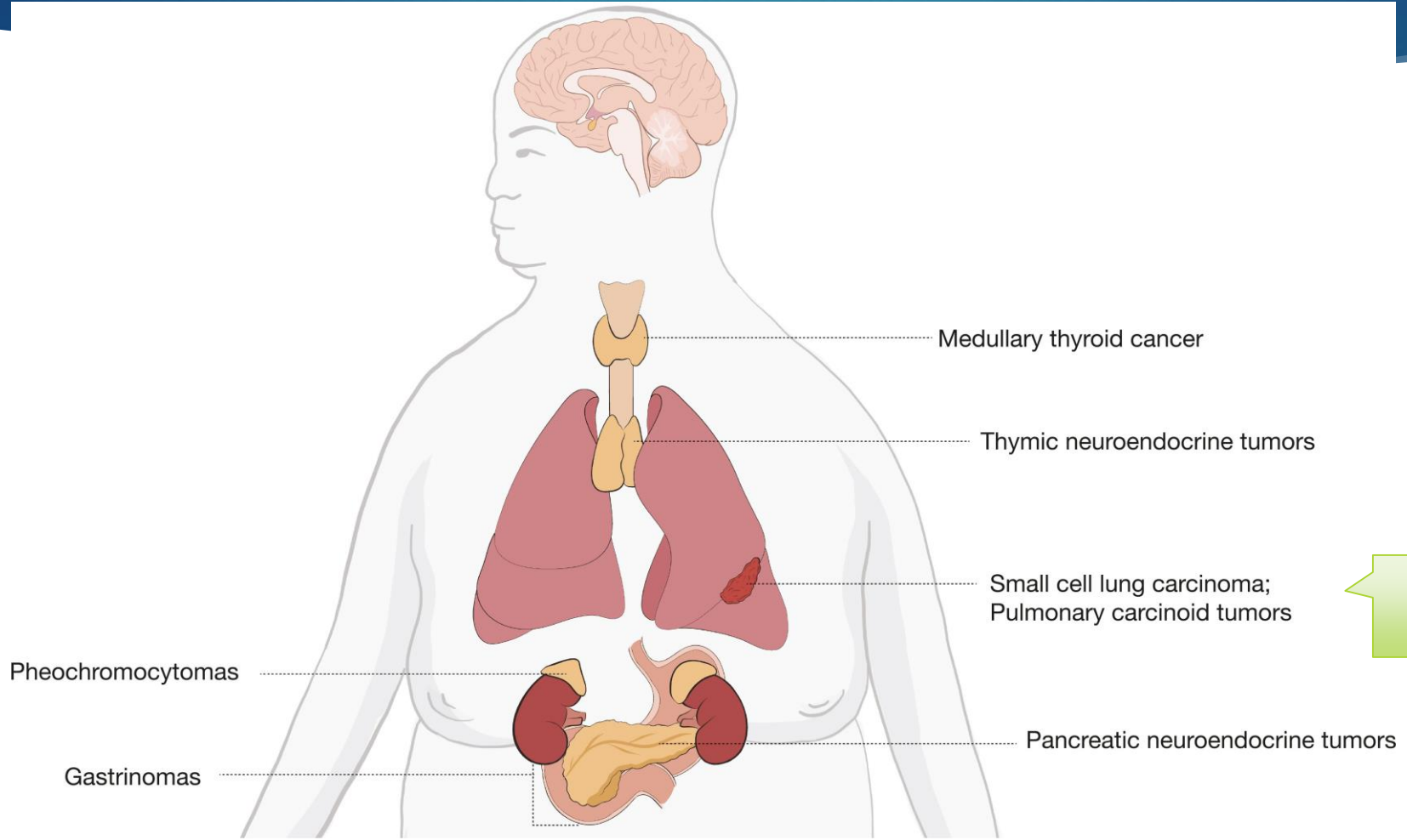
local metabolism by 11β-HSD and 5α-reductase

ACTH-dependent CS

- ACTH levels will be inappropriately normal or elevated (generally > 20 pg/mL) in ACTH-dependent causes and low (generally < 10 pg/mL) ACTH-independent causes of CS.
- ACTH-dependent CS comprises 80% to 85% of all CS cases.
- Thirty percent of the patients with CS have ACTH levels in the "gray zone" (5-20 pg/mL) and should have repeat testing and consideration of adrenal imaging to detect possible adrenal pathology.

Ectopic ACTH Secretion

20%



most common

Differentiation Between Cushing disease and Ectopic ACTH Secretion

- conventional MRI, which can only detect 36% to 63% of pituitary microadenomas in patients with Cushing disease
- high-resolution 3T-MRI is characterized by thinner sections and superior soft-tissue contrast and can detect adenomas as small as 2 mm.
- a pituitary adenoma > 6 mm is found on MRI, the need for further testing with BIPSS is not necessary.
- But MRI can be negative in up to 40% to 60% of Cushing disease cases; it false-positive EAS.

differentiate between Cushing disease and EAS

- **BIPSS** is the **gold standard**
- High Sensitivity by obtaining ACTH levels under CRH stimulation.
- elevated IPS-to-peripheral (IPS:P) ACTH ratios: > 2 pre-CRH stimulations or > 3 post-CRH stimulations.
- A lack of an IPS:P ACTH gradient suggests an ectopic source

A novel imaging

- A noninvasive imaging for corticotroph adenomas using Gallium-68 (68Ga)-tagged CRH combined with PET-CT.
- 68Ga-tagged CRH can be used to detect CRH receptors, which are upregulated on corticotroph adenomas.
- the size of the study was small, 68Ga CRH PET-CT scan was able to correctly identify 100% of Cushing disease cases less than 6 mm in size
- This technique is still investigational and not currently widely available

Dynamic testing with can also be used to help differentiate between CD and EAS

- high-dose DST
- CRH test

After CRH ACTH>50%
Cortisol>20%
In CD ; bronchial carcinoid

- desmopressin testing

+ in ACTH adenoma (V2R)
V3R EAC

type of ectopic tumor , age, sex, severity of hypercortisolism

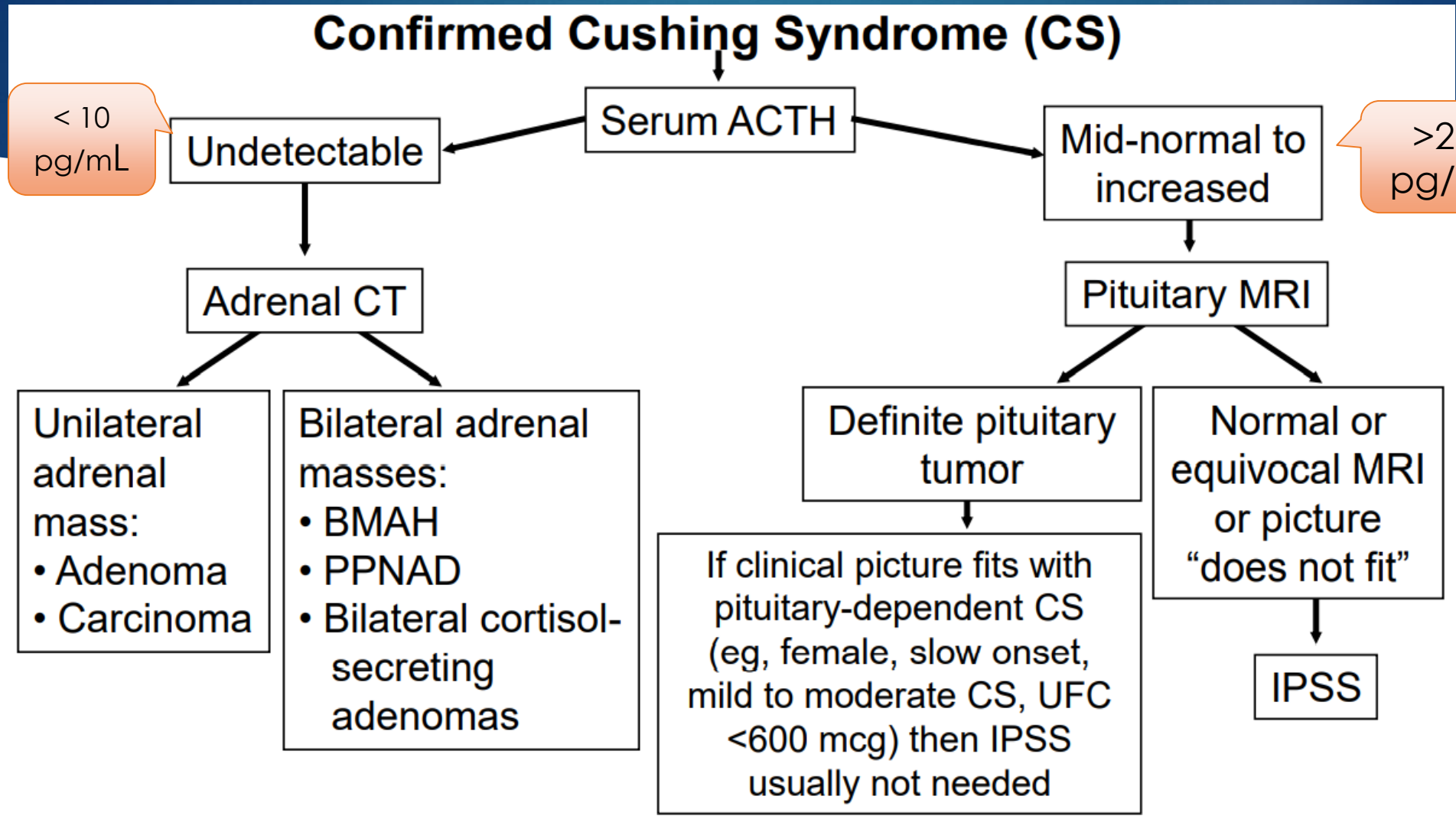
none of these tests have 100% specificity because if high false-positive rates, and results can be discordant in up to 65% of patients

- In cases of discordant results, BIPSS is needed
- In cases in which results are inconclusive for Cushing disease, evaluation for EAS should be considered
- Whole-body thin-slice CT scans
- Second-line tests include functional imaging using 68Ga-PET/CT or 18FDG PET/CT scans

ACTH-independent CS

- adrenal adenoma usually
- less frequently by bilateral micro- or macronodular adrenal hyperplasia
- adrenal carcinoma rarely
- primary pigmented nodular adrenocortical disease
- the Carney complex
- McCune-Albright syndrome

Very rare causes


Confirmed Cushing Syndrome (CS)
Serum ACTH
< 10 pg/mL
Undetectable
Mid-normal to increased
>25 pg/ml
Adrenal CT
Pituitary MRI
Unilateral adrenal mass:
• Adenoma
• Carcinoma
Bilateral adrenal masses:
• BMAH
• PPNAD
• Bilateral cortisol-secreting adenomas
Definite pituitary tumor
Normal or equivocal MRI or picture "does not fit"
If clinical picture fits with pituitary-dependent CS (eg, female, slow onset, mild to moderate CS, UFC <600 mcg) then IPSS usually not needed
IPSS

adrenal mass

- tumor >4 cm
- Calcifications
- irregular margins
- HU> 20)

} worrisome features

- and/or the plasma steroid profile shows elevated DHEAS and steroid precursors an additional FDG-PET scan can guide the decision on an (open) adrenalectomy with an oncological approach.

mild autonomous cortisol secretion (MACS)

- A subgroup of ACTH-independent hypercortisolism involves patients with uni- or bilateral adrenal incidentaloma(s) and mild autonomous cortisol secretion (MACS)
- cushingoid features
- Hypertension
- type 2 diabetes
- Obesity
- Dyslipidemia
- atrial fibrillation
- and psychiatric or neurocognitive symptom

increased risk of frailty, osteoporosis, cardiovascular morbidity, and mortality

mild autonomous cortisol secretion (MACS)

- 1-mg DST is up to 100% sensitive, so it can be used as an optimal first-line screening test
- in patients post-DST cortisol levels are related to cardiovascular events and all-cause mortality
- Low or suppressed ACTH values can further indicate autonomous cortisol production

Clinical diagnosis of CS in Pregnancy

- CS is rarely diagnosed during pregnancy
- predominant etiology of CS in pregnant patients is adrenal adenomas, found in 40% to 60% of cases
- Early diagnosis and management of CS during pregnancy are important because of associated fetal and maternal morbid
- the diagnosis of CS during pregnancy can be more challenging because of overlap in features of hypercortisolism and classic features of pregnancy

pregnant patients have a triad of HTN, skin ecchymosis, and muscle atrophy, CS should be considered

Biochemical diagnosis of CS in pregnancy

- Normal physiologic changes
- activation of the HPA axis
- Starting in the first trimester,
  - increase in estrogen → ↑ CBG
  - CRH produced by the placenta → ↑ ACTH

increase in total plasma cortisol

Pitfalls in diagnosis of CS in pregnancy

- Suppression of serum cortisol by dexamethasone is blunted during pregnancy

DST diffcult to interpret

- UFC is often the recommended screening test during pregnancy

challenges to this as well

- During the second trimester, UFC increases, 1.4-fold increase during the second trimester
- a 1.6-fold increase during the third trimester

- UFC can be unaffected during the first trimester,
- it may **not be** a reliable diagnostic test in the second and third trimesters, unless levels are significantly increased
- LNSC levels during pregnancy, there have been some studies looking at defining normal threshold values in each trimester of pregnancy, which could lead to increased use in screening these patients

Case 1

- A 45 y/o woman was referred to the University Medical Center from another hospital for possible Cushing syndrome
- weight gain of 6 kg in 18 months
- central obesity
- moderate muscle weakness
- Insomnia
- Hypertension had been diagnosed 3 years ago and was treated with nifedipine 30 mg.

- She consulted a psychiatrist for 14 months because of depressive complaints and there was suspicion of bipolar disorder. For this, she is treated with carbamazepine 200 mg twice daily.
- There is no alcohol or drug abuse.

Drug hx :

- nifedipine 30 mg
- carbamazepine 200 mg twice daily

carbamazepine was replaced by lithium

Lab data

- UFC was found of 2 times ULN
  - 6 weeks later revealed a UFC of 1.5 to 2.0 times ULN
- 1-mg DST with a cortisol value of 5.62 µg/dL
  - 3.05 µg/dL
- a high normal ACTH level of 40.9 pg/mL (ULN 50 pg/mL)
  - LNSC 0.047 and 0.065 µg/ dL
- Pituitary imaging with magnetic resonance imaging (MRI) showed a small cystic lesion at the left side of the pituitary
  - Dex_CRH → undetectable cortisol

A pseudo-Cushing syndrome secondary to her psychiatric disorder

Learning Points

- CS is multisystemic disease with serious morbidity and mortality and the diagnosis should preferably be made at an early stage considering long-term complications

- In patients with (mild) ACTH-dependent CS, a pseudo-CS should always be considered.

- The results of first-line screening tests for Cushing syndrome can be influenced by the use of concomitant medication

- LNSC and the second-line dexamethasone-CRH test can be useful to differentiate pseudo-Cushing syndrome from ACTH-dependent Cushing syndrome

Correlation increase reliability

- For increased reliability using correlation finding (in clinical evaluation and lab data
- ACTH
- DHEAS
- DHEA
- Cortisol
- UFC
- Potassium
- Adrenal hyperplasia
- Size of adenoma
- …

Easy bruising , Thin skin ,striae

THANKS FOR YOUR ATTENTION