



THE UNIVERSITY OF
CHICAGO
MEDICINE &
BIOLOGICAL
SCIENCES

28 F presenting with weight gain

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Adult Endocrinology Fellow
October 30th, 2024

CME: Text LOMCER to 773-245-0068

Objectives

- Discuss biochemical screening tests for Cushing's syndrome
- Differentiate Cushing's disease from ectopic ACTH-dependent Cushing's syndrome
- Discuss signs of clinical remission and post-surgical management



HPI

- 28 F self-referred to endocrinology for weight gain and concern for Cushing's.
- Breast fed child for 3 years, weaned this past year. Weight increased from 108 lbs to 158 lbs (50 lb weight gain) in the past year.
- Endorses hair loss, facial fullness, and flushing.
- Menstrual cycle has become irregular, periods every 1-2 months, consisting of 4-5 days bleeding.
- Stress fracture of foot 5 weeks ago from walking



History and Physical Exam

Medical:

- None

Surgical:

- Wisdom teeth removal

Family:

- Mother: HTN
- Father and sister: kidney stones
- Cousin: Hashimoto's hypothyroidism

Social:

- Mom
- Works 15 hr/week conference planning
- Seldom EtOH use
- Non-smoker

Medications:

- No prescription meds
- Thyroid supplement
- Liver supplement
- B complex
- Multivitamin

Exam

Recent Vitals: T 36.8, HR 77, BP 136/86, RR 18, SpO2 99%, Wt 158 lbs, Ht 5' 7", BMI 24.9 kg/m²

Virtual visit-

General: No acute distress

HEENT: facial fullness

Pulm: no work of breathing

Skin: purple stretch marks in armpit and legs

Neuro: A&Ox3



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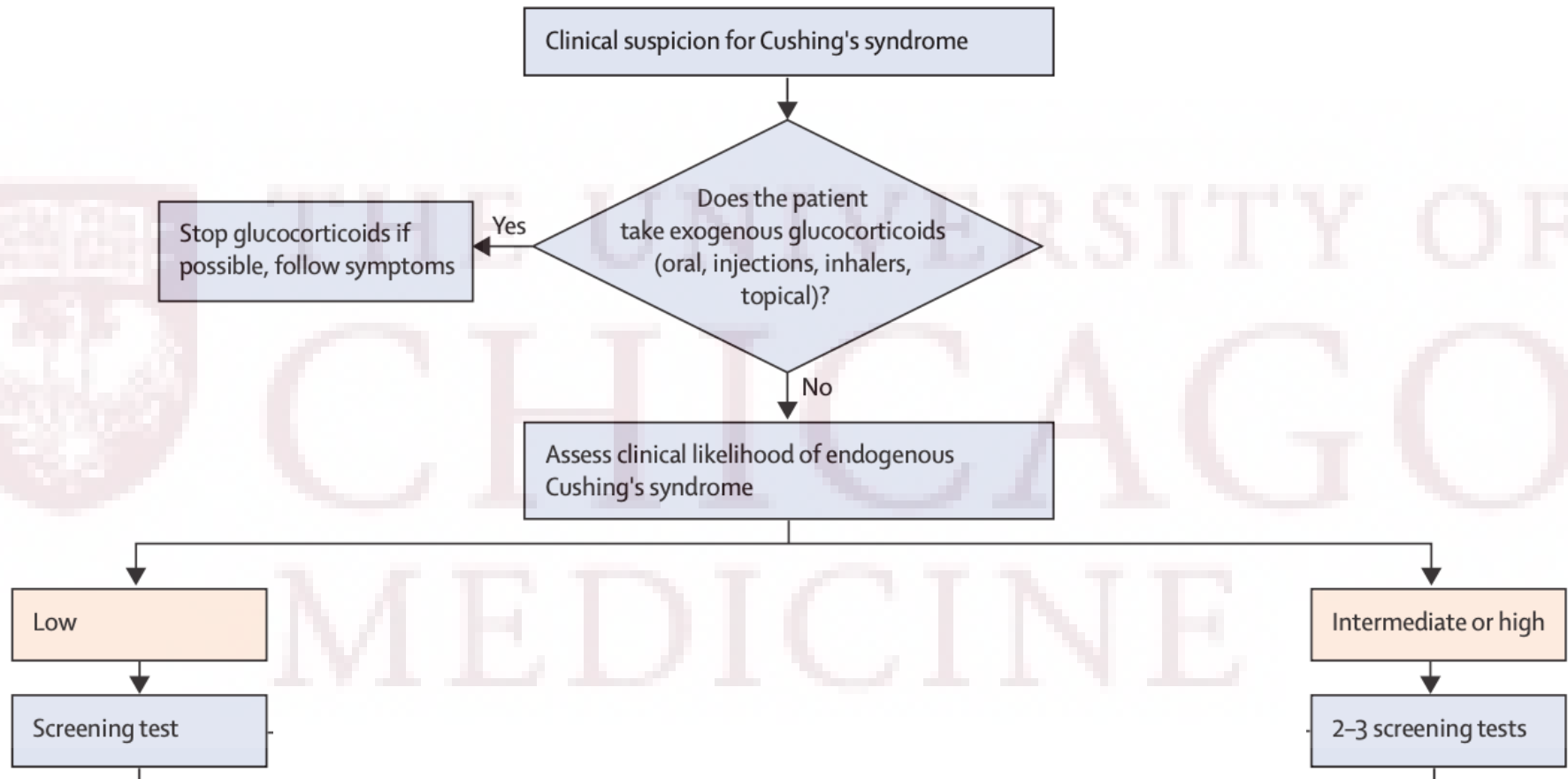
Skin: purple stretch marks in armpit and legs

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What is in your differential for weight gain?
Which labs would you like?



Pituitary Society Consensus - Cushing's Disease (Oct 2021)

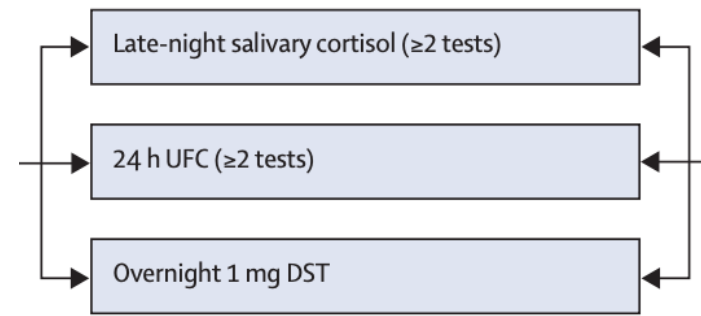


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graph TD; Q1{Does the patient take exogenous glucocorticoids (oral, injections, inhalers, topical)?} -- Yes --> A1[Stop glucocorticoids if possible, follow symptoms]; Q1 -- No --> A2[Assess clinical likelihood of endogenous Cushing's syndrome]; A2 --> B1[Low]; A2 --> B2[Late-night salivary cortisol (≥2 tests)]; A2 --> B3[Intermediate or high]; B1 --> C1[ ]; B2 --> C2[ ]; B3 --> C3[ ]; style C1 fill:none,stroke:none; style C2 fill:none,stroke:none; style C3 fill:none,stroke:none;
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The flowchart outlines the diagnostic approach for Cushing's syndrome. It begins with a decision point: 'Does the patient take exogenous glucocorticoids (oral, injections, inhalers, topical)?'. If 'Yes', the instruction is to 'Stop glucocorticoids if possible, follow symptoms'. If 'No', the next step is to 'Assess clinical likelihood of endogenous Cushing's syndrome'. This assessment leads to three possible outcomes: 'Low', 'Late-night salivary cortisol (≥2 tests)', or 'Intermediate or high'. The 'Low' and 'Intermediate or high' outcomes lead to further diagnostic steps (indicated by arrows pointing down), while the 'Late-night salivary cortisol (≥2 tests)' outcome leads to a further diagnostic step (indicated by an arrow pointing right).



Screening Tests Instructions



- **Late night salivary cortisol x2**

- Cortisol secretion follows diurnal variation, peaks at 8 AM, nadir at 10 PM
- Sensitivity high 80-90%, specificity 70-90%
- Not dependent on cortisol binding globulin (CBG), which can be affected in pregnancy or critical illness

- **24-hour urinary cortisol**

- 8 AM to 8 AM collection, refrigerate samples during collection
- Sensitivity 53-90%, specificity 79-90%, wide variability between studies
- Also not dependent on CBG

- **1-mg dexamethasone suppression test**

- Take 1 mg dexamethasone at 11 PM to suppress endogenous ACTH and check 8 AM cortisol, normal response cortisol < 1.8 mcg/dL
- Sensitivity 87%, specificity 100%



Labs (brought from outside lab):

- CMP:
 - Na 142, K 4.2 Cl 103, Co2 28, BUN 12, Cr 0.86, Glucose 93
 - Ca 9.7, Alb 4.6, TP 6.5
 - AST 26, ALT 40, ALP 59, Tbili 0.7
- CBC: WBC 8.6, Hgb 15, Plt 279
- TSH 1.29, FT4 1.2
- Anti-TPO <12, anti-TG 13.2 (wnl)
- Cortisol (7 AM) 16.5

Hormones		
Test Name	Current	Reference Range
Estradiol (pg/mL)	28.4	
FSH (mIU/mL)	4.6	
DHEA-S (µg/dL)	273.0	98.8~340.0
SHBG (nmol/L)	14.6 L	24.6~122.0
Cortisol (µg/dL)	16.5 H	A.M.: 6.2-19.4 P.M.: 2.3-11.9
Testosterone, Total (ng/dL)	22.1	6.9~71.7
Free Testosterone (ng/dL)	0.56	0.04~0.95
Progesterone (ng/mL)	0.260	
Prolactin (ng/mL)	14.10	4.79~23.30



Additional Labs:

- Cortisol/ACTH
 - 7 AM total cortisol - **30.9** (RR 4-22) mcg/dL, ACTH - **63** (RR 6-50) pg/mL
 - 11 PM salivary cortisol x2 - **0.3, 1.58** (ULN <0.09) mg/dL
 - 24-hour urine free cortisol - **432.7** (RR 4-50) mcg/24h

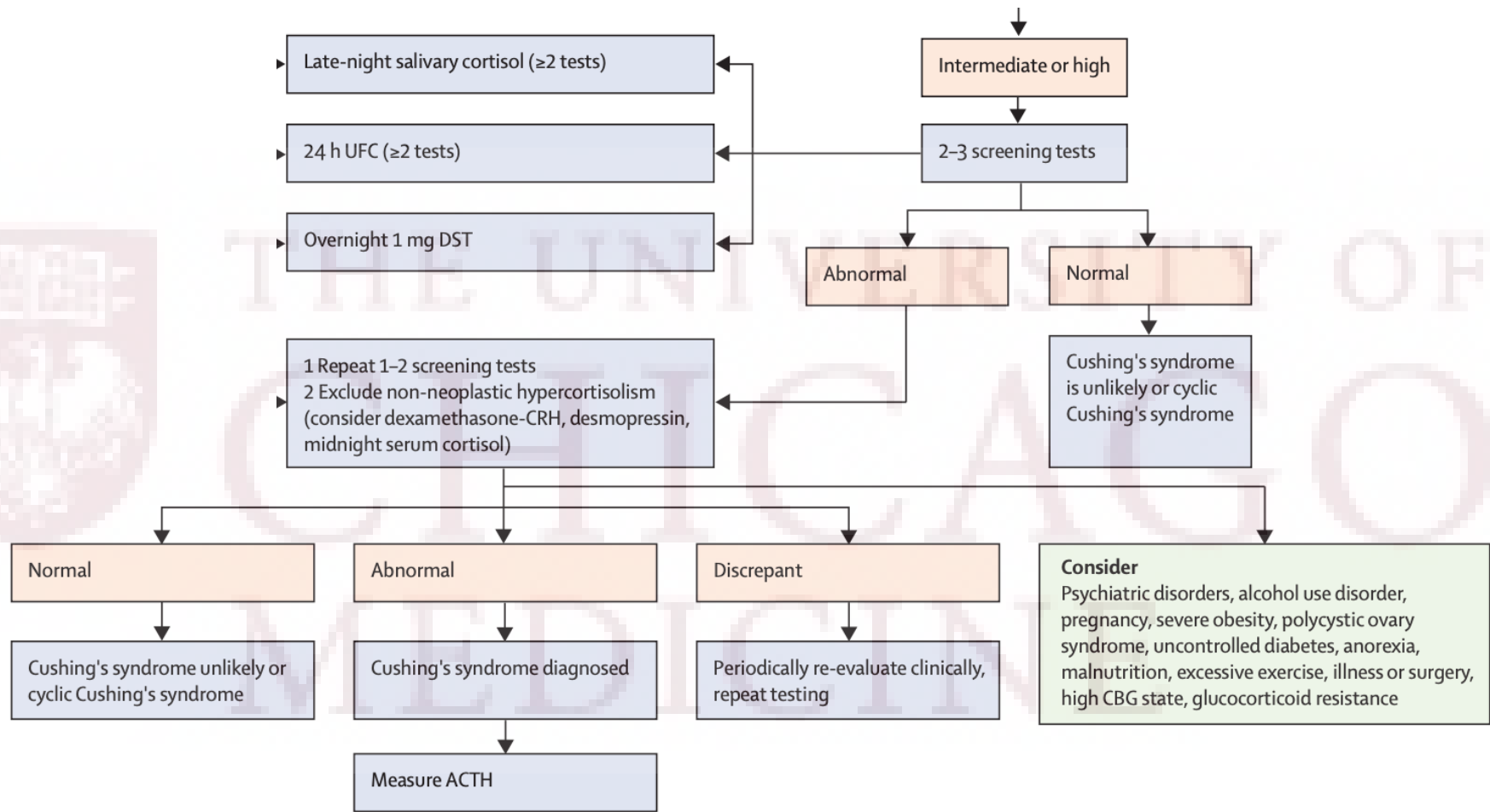


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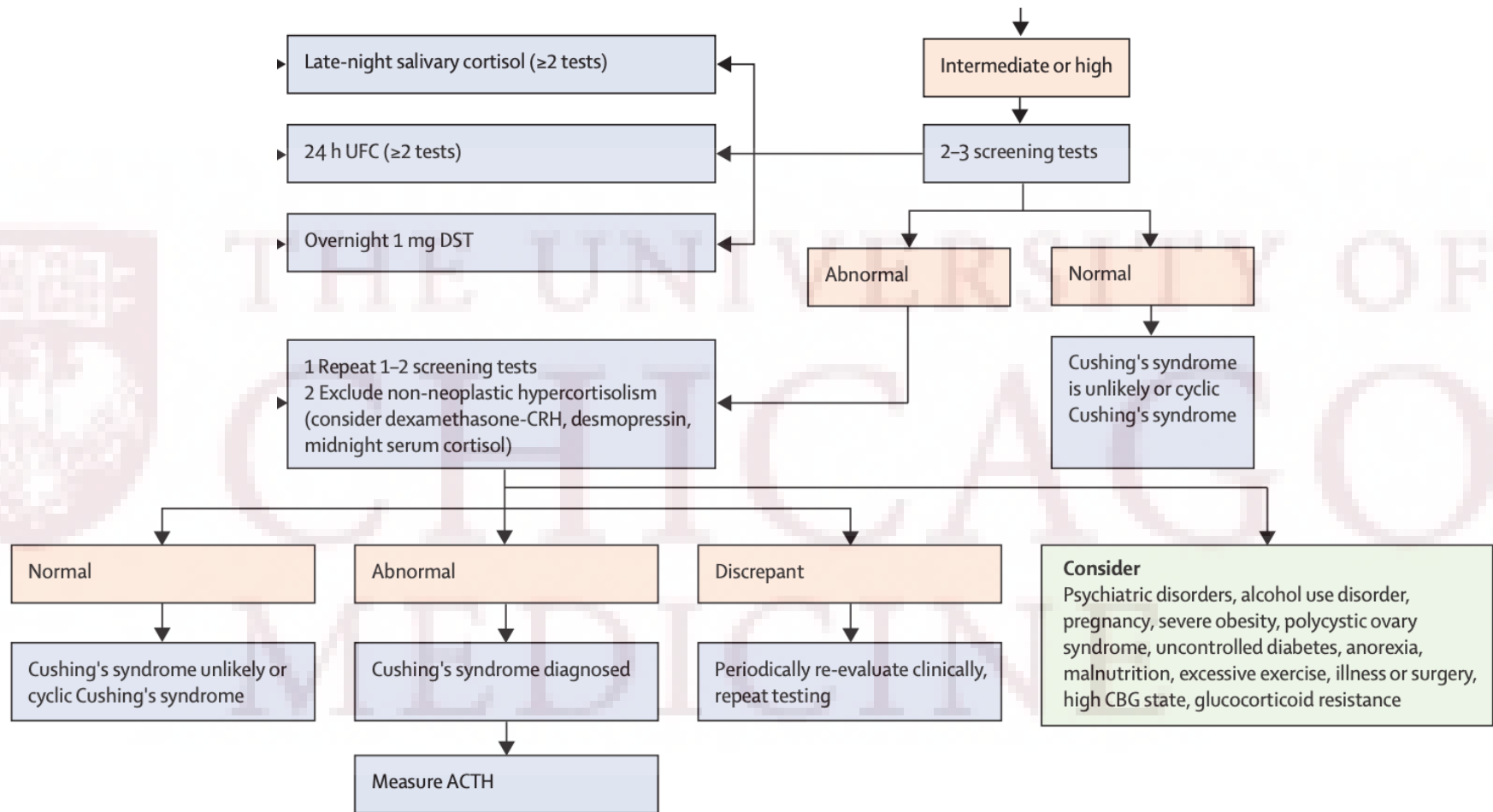
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- Prolactin 9.92
- FSH 5, LH 11.4
- IGF-1 464 (Z-score >3 SD), GH 0.10 (low)
 - 2 hour glucose tolerance test: GH - 1.69 (0 hrs) -> 0.29 (2 hrs); RR (0.13 - 9.88 ng/mL)
- B-HCG negative



Pituitary Society Consensus - Cushing's Disease (Oct 2021)



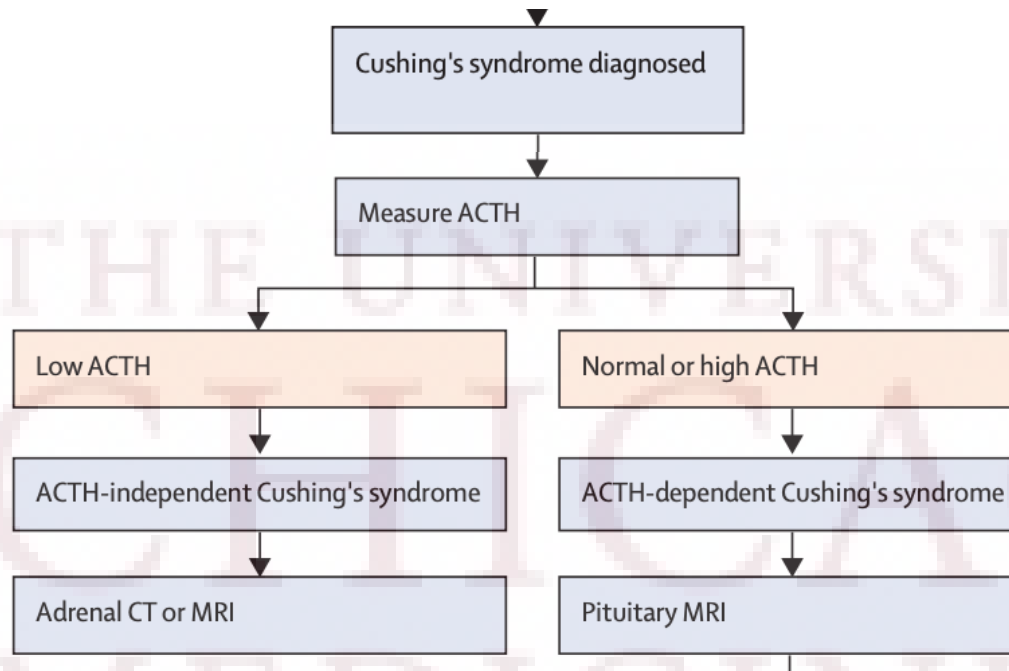
Pituitary Society Consensus - Cushing's Disease (Oct 2021)



What is the next step you would take in diagnosis?



Pituitary Society Consensus - Cushing's Disease (Oct 2021)



Imaging considerations

- MRI pituitary is main imaging choice for ACTH secreting pituitary adenomas
- Approximately 1/3 of scans can be negative in Cushing's disease
- Note that tumor size does not necessarily correlate with degree of hypercortisolism



MR Pituitary

FINDINGS: Dedicated images through the sella demonstrate a normal size of the pituitary gland. There is a **hypoenhancing lesion in the right inferior mid aspect of the pituitary gland measuring approximately 4 x 6 x 2 mm** in the AP, transverse, and craniocaudal dimensions. This is suspicious for microadenoma. No other abnormal signal intensity or mass is seen within the pituitary gland. The pituitary stalk lies in the midline.

IMPRESSION: A subcentimeter lesion in the right inferior aspect of the pituitary gland is suspicious for pituitary microadenoma.



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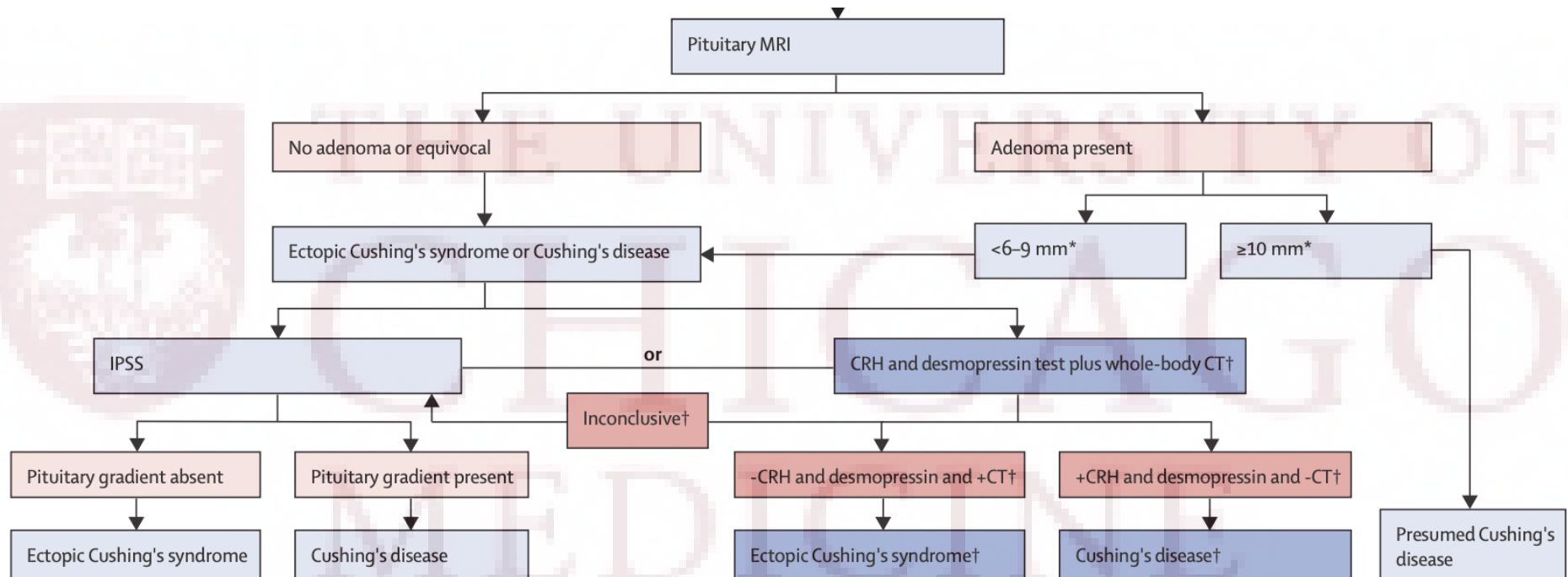
IMPRESSION: A subcentimeter lesion in the right inferior aspect of the pituitary gland is suspicious for pituitary microadenoma.



Case closed! Or is it?



Pituitary Society Consensus - Cushing's Disease (Oct 2021)



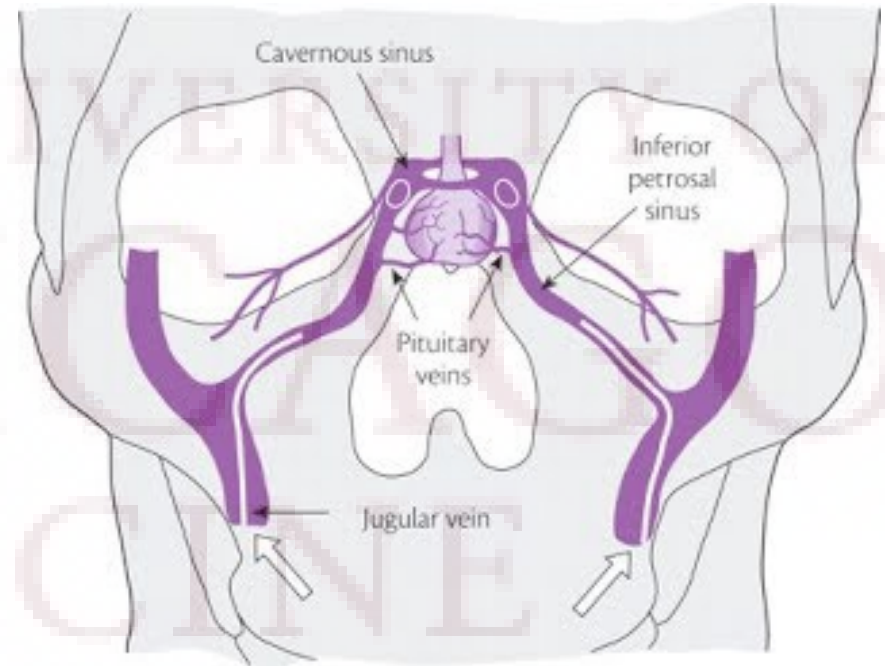
Cushing's Disease vs Ectopic ACTH-dependent Cushing's

- Cushing disease (central):
 - Glucocorticoid receptors retain ability to inhibit ACTH secretion in presence of high dexamethasone doses
 - ACTH secreting adenomas overexpress Vasopressin V2 and V1b (V3) receptors
 - Also overexpress CRH receptor
- ACTH-secreting tumors (ectopic):
 - Glucocorticoid, vasopressin, and CRH receptors are not typically expressed
 - Some well-differentiated neuroendocrine tumors can express these receptors
- Inferior petrosal sinus sampling (IPSS), Dexamethasone-CRH test, or Desmopressin stimulation test can be used to differentiate these



Inferior petrosal sinus sampling (IPSS)

- Inferior petrosal sinus drains venous blood from the pituitary
- Only use in setting of hypercortisolemia (may do repeat 24-hr UFC the day before to confirm), since ACTH should be suppressed
- If ACTH in this area is higher than peripheral, then suggests pituitary as cause of excess
- Direct stimulation of pituitary corticotrophs with CRH increases sensitivity
- Cannot lateralize the lesion

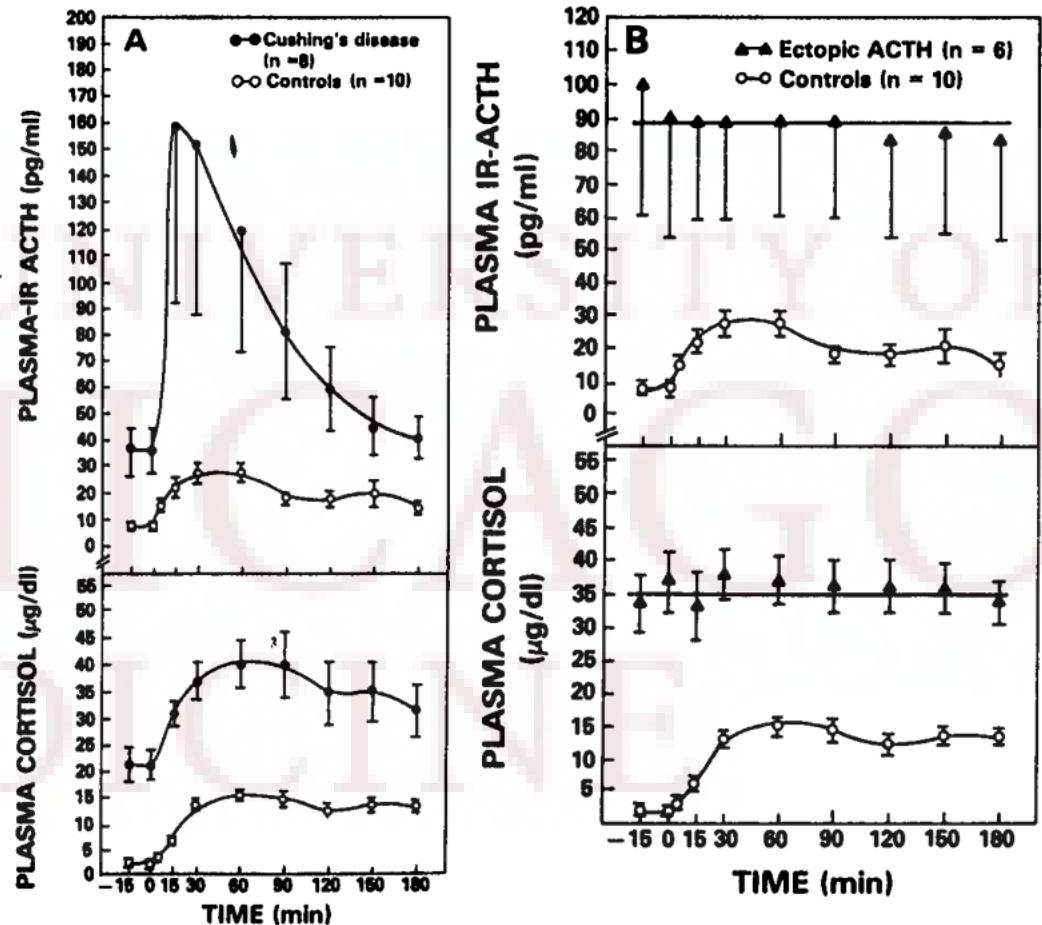


Dexamethasone-CRH Stimulation Test

- Dexamethasone administered evening before
- Baseline cortisol and ACTH checked
- CRH 1ug/kg given via IV
- Cortisol and ACTH checked at set intervals over 210 minutes

In Cushing's disease:

- ACTH should rise at 15 and 30 minutes by at least 35%
 - 93% sensitive, 100% specific
- Cortisol should rise at 30 and 45 minutes by at least 20%
 - 91% sensitive, 88% specific



DDAVP Stimulation Test

- ACTH-secreting adenomas overexpress V1b vasopressin receptors
- Desmopressin will cause increase in plasma ACTH after injection
- High specificity for Cushing's disease
- Less complex and expensive than CRH stim

DDAVP Stimulation Test

Purpose: To distinguish the cause of Cushing's syndrome and/or to rule out pseudo-Cushing's

The test can be given with or without Dexamethasone. If dexamethasone given, 1 mg dexamethasone should be prescribed by ordering provider. Patient should take this at 11 PM the night prior to the test.

Patient should fast overnight. Patient should present by 8:00 AM.

RN to place IV for blood draws and draw samples for ACTH and Cortisol at the below intervals. Please label samples with the time (minus 15, baseline, 15 min, 30 min, 45 min, etc).

You can use the below table to keep track of samples that have been drawn and when.

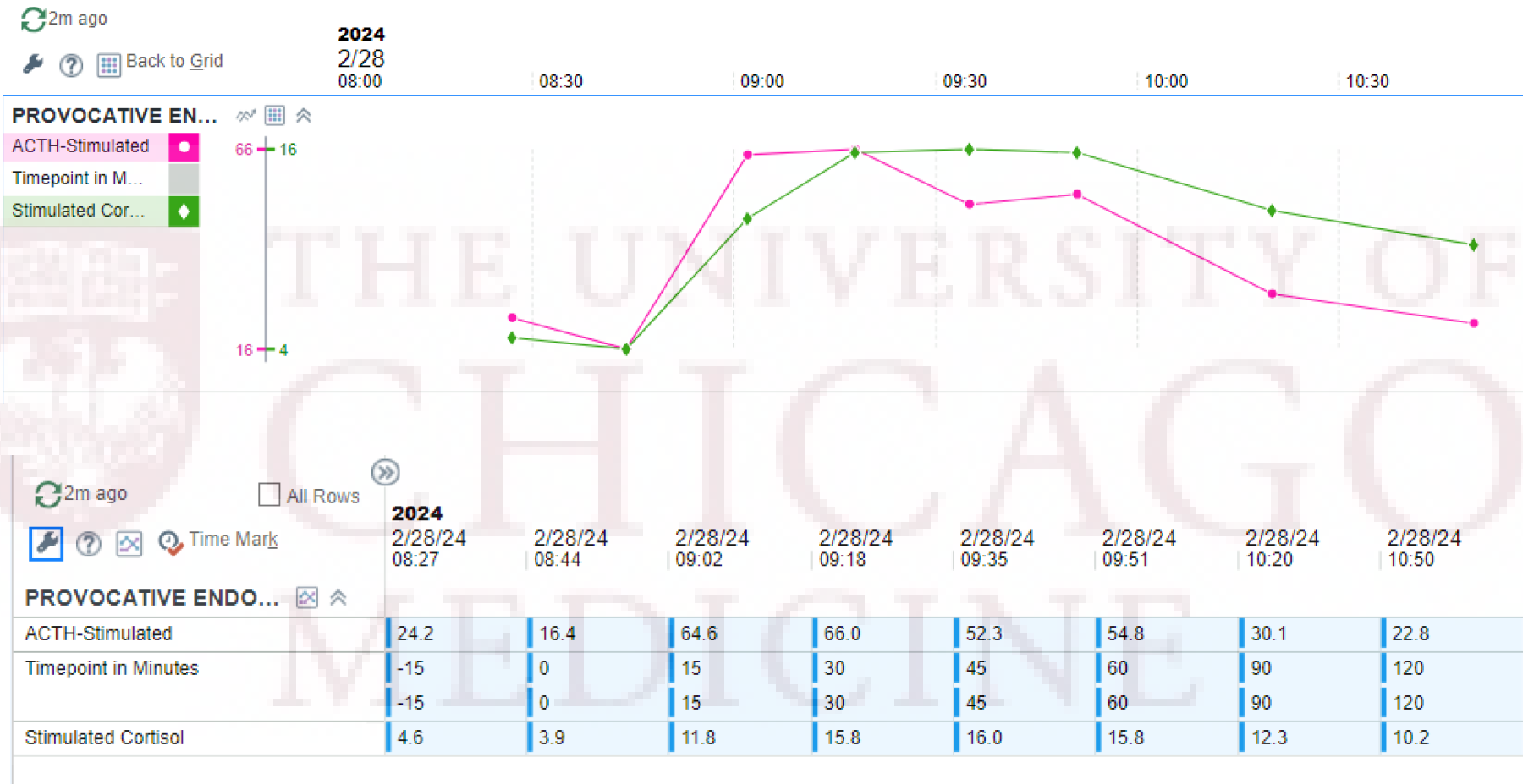
Time	ACTH	Cortisol
Minus 15 minutes (Prior to DDAVP)		
Baseline – Immediately Prior to DDAVP		
Give DDAVP 10 mcg IV		
15 minutes		
30 minutes		
45 minutes		
60 minutes		
90 minutes		
120 minutes		

After the final blood draw, remove IV and patient can leave.

Notify ordering provider that the test is complete.



Additional Workup: DDAVP Stim Test



Treatment – Underwent endoscopic endonasal transsphenoidal resection of pituitary microadenoma

		2024						
		4/16/24 15:26	4/16/24 22:19	4/17/24 03:59	4/17/24 09:02	4/17/24 15:20	4/17/24 19:40	4/17/24 20:59
ENDOCRINOLOGY								
ACTH				21.0				
Cortisol		27.6	54.2	17.0	5.7	2.5	1.9	1.7

- Cortisol level monitored post-surgery and fell – “cortisol crash”
- Transient diabetes insipidus for several days post-op, since resolved



Pathology:

- “Histologic sections show pituitary tissue that includes anterior pituitary parenchyma with a nested arrangement and a random admixture of cells with different cytoplasmic staining. The staining patterns of the pituitary hormones (i.e. ACTH, TSH, Prolactin, LH, GH, and FSH) and SF-1 demonstrated a fairly randomly admixed population of all cell types. Both the anterior and posterior pituitary tissue demonstrate diffuse positive staining for synaptophysin and the anterior pituitary tissue stains for CAM5.2.
- **There are no areas of a distinct clonal cluster and the special stains don't identify a distinct cluster of ACTH positive cells. Clinical correlation with the post-procedural labs will be critical. ”**

Clinically:

- Clinical remission of Cushing's symptoms
- Continued on HC 15/5 mg in the morning and afternoon



Post-surgical considerations

- Post-surgical transient AI is expected
- Post-surgery AM cortisol predicts remission
 - <1.8 ug/dL very likely, <5 ug/dL likely, >7.2 ug/dL persistent disease
 - Less data for late night salivary cortisol and DDAVP testing, but may be helpful
- Probability of adrenal function recovery:
 - Ectopic 82% - median recovery time 0.6 years
 - Cushing's disease 58% - median recovery time 1.4 years
 - Adrenal Cushing's syndrome 38% - median recovery time 2.5 years



Take Home Points

- Biochemical screening tests for Cushing's syndrome include 11 PM salivary cortisol x2, 24 hour urine free cortisol x2, and 1-mg dexamethasone suppression test
- Cushing's disease and ectopic ACTH-dependent Cushing's syndrome can be differentiated using IPSS, CRH-dexamethasone, or DDAVP stimulation testing
- After transsphenoidal adrenalectomy, expect transient post-operative adrenal insufficiency, and low AM cortisol predicts remission

Special thank you to Dr. Rajesh Jain!



References

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ENDORAMA

December 12, 2024

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