THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

“26 year old woman with amenorrhea”

26 year old woman with amenorrhea

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Objectives

- Discuss causes of primary amenorrhea
- Discuss causes of elevated DHEA-S level
- Discuss clinical management and follow up of [redacted]

Initial Presentation

- 26 year old woman referred to Endocrinology clinic by Gynecology for elevated DHEA-S levels

- She has a history of primary amenorrhea
  - In 2011 she presented to her college student health with primary amenorrhea and hair loss from the scalp
  - Otherwise had normal growth and development
  - No other significant medical history

Primary amenorrhea workup

- Hormonal evaluation (2011)
  - TSH 0.84
  - FSH 10.2
  - LH 2.9
  - Prolactin 8.9
  - Testosterone 30
  - Estradiol 24
- Pelvic ultrasound unremarkable

Follow up

- No further workup was done
- Based on hair loss and history of amenorrhea, she was told she had PCOS
- Started on OCP -> regular menses, improved hair loss

Initial visit at U of C

- Moved to Chicago for graduate school in 2016
- Patient went to gynecologist for routine check up in 1/2016
- Evaluation found an elevated DHEAS ~400 with repeat level ~500.
- Testosterone levels are not elevated but she is on an OCP

	1/25/16 1736	3/24/16 1349
LH	4.3	
FSH	7.3	
Prolactin	15.22	
Te binding globulin	145	
Total testosterone	38	
Free testosterone	4	
DHEA-S	464.1	557.4

Next steps?

CT abdomen/pelvis

ABDOMEN:

LUNG BASES: No significant abnormality noted.

LIVER, BILIARY TRACT: Liver is normal in morphology. Hypodense left lateral segment lesion shows delayed enhancement on the 15 minute delay likely represents a hemangioma. Additional subcentimeter hypodense foci too small to characterize. Hepatic and portal veins are patent. No biliary ductal dilatation.

SPLEEN: No significant abnormality noted.

PANCREAS: No significant abnormality noted.

ADRENAL GLANDS: Adrenal glands are normal in morphology. No focal adrenal lesion is identified.

KIDNEYS, URETERS: No significant abnormality noted.

RETROPERITONEUM, LYMPH NODES: No retroperitoneal lymphadenopathy or masses.

CALCIFICATIONS IN ABDOMINAL AORTA AND ITS BRANCHES: None

BOWEL, MESENTERY: No significant abnormality noted.

BONES, SOFT TISSUES: No significant abnormality noted.

OTHER: No significant abnormality noted.

PELVIS:

UTERUS, ADNEXA: No significant abnormality noted.

BLADDER: No significant abnormality noted.

LYMPH NODES: No significant abnormality noted.

BOWEL, MESENTERY: No significant abnormality noted.

BONES, SOFT TISSUES: No significant abnormality noted.

OTHER: No significant abnormality noted.

IMPRESSION:
1. No focal adrenal mass.
2. If patient has persistent elevation of DHEAS consideration should be made for a whole body nuclear medicine exam for evaluation.

*Adrenal imaging indicated to look for adrenal mass for DHEA-S levels >700
Derksen J et al. NEJM 1994;331:968

Initial endocrinology visit

- In 5/2016, the patient presents to endocrinology clinic for the elevated DHEA-S levels
  - Continues on OCP
  - Gained 30 pounds since originally started on OCP
  - Hair loss improved
  - Denies hirsutism or acne
  - Denies any bruising, muscle weakness, or prolonged bleeding
  - Denies history of glucose intolerance or hypertension
- Vitals: afebrile, BP 117/89, pulse 82, RR 18, BMI 27.13
- Exam:
  - Acanthosis nigricans present under arms
  - Mild hair loss from scalp
  - No severe hirsutism or acne or dorsocervical fat pad
  - Few nonpigmented striae

	1/25/2016 1736	3/24/2016 1349
ENDOCRINOLOGY		
DHEA-S	*464.1 ** ▲	*557.4 ** ▲

Causes of adrenal hyperandrogenism

Primary adrenal diseases
Premature adrenarche
Adrenal tumors (adenomas, carcinomas, bilateral macronodular adrenal hyperplasia)
ACTH hypersecretion
Congenital adrenal hyperplasia
ACTH-dependent Cushing's syndrome
Glucocorticoid resistance
Cortisone reductase deficiency
Hyperprolactinemia
Exogenous
Androgens
Pregnancy
Placental sulfatase deficiency (no hyperandrogenism)
Placental aromatase deficiency (mother and female fetus virilization)
P450 oxidoreductase deficiency
Other
PAPSS2 deficiency (apparent DHEA sulfotransferase deficiency)

ACTH: corticotropin; DHEA: dehydroepiandrosterone.

ACTH stim test

- To evaluate for nonclassical CAH

	0 minutes	30 minutes	60 minutes
17-hydroxyprogesterone	43	99	101
DHEA-S	429.3		483.3
Cortisol	58.9	70.8	81.6
ACTH	62.6		

Subsequent endo visit

- 6/2016 visit
  - 17-OH progesterone levels were not elevated, nonclassical CAH ruled out
  - Unexpected high cortisol levels in response to ACTH stimulation
  - Combined OCP can elevate CBG level due to estrogen content causing elevation of total cortisol level. However, the cortisol levels were very high (~80ug/dl)
  - Cushing's syndrome suspected, workup ordered
    - 24 hour UFC
    - Late evening salivary cortisol
    - Morning ACTH ordered

Workup

- Cortisol 32.8
- ACTH 25.8
- Saliva cortisol 110ng/dL (reference range <100)
- 24 hour urine cortisol 36 (reference range 3.5 – 45)
- HbA1c 5.3%

Thoughts?

Establishing Cushing's diagnosis

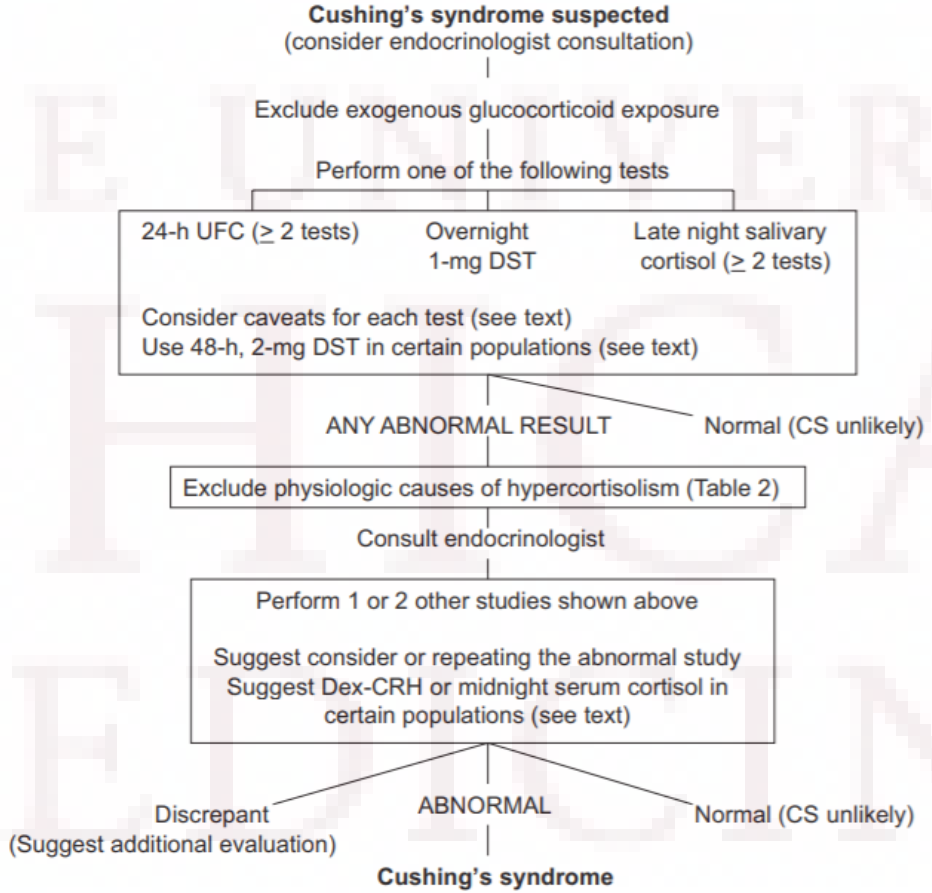


FIG. 1. Algorithm for testing patients suspected of having Cushing's syndrome (CS). All statements are recommendations except for those prefaced by suggest. Diagnostic criteria that suggest Cushing's syndrome are UFC greater than the normal range for the assay, serum cortisol greater than 1.8 μg/dl (50 nmol/liter) after 1 mg dexamethasone (1-mg DST), and late-night salivary cortisol greater than 145 ng/dl (4 nmol/liter).

Drugs that interfere with testing

TABLE 3. Selected drugs that may interfere with the evaluation of tests for the diagnosis of Cushing's syndrome[a]

Drugs
Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4
Phenobarbital
Phenytoin
Carbamazepine
Primidone
Rifampin
Rifapentine
Ethosuximide
Pioglitazone
Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4
Aprepitant/fosaprepitant
Itraconazole
Ritonavir
Fluoxetine
Diltiazem
Cimetidine
Drugs that increase CBG and may falsely elevate cortisol results
Estrogens
Mitotane
Drugs that increase UFC results
Carbamazepine (increase)
Fenofibrate (increase if measured by HPLC)
Some synthetic glucocorticoids (immunoassays)
Drugs that inhibit 11β-HSD2 (licorice, carbenoxolone)

[a] This should not be considered a complete list of potential drug interactions. Data regarding CYP3A4 obtained from http://medicine.iupui.edu/flockhart/table.htm.

Repeated testing

- Saliva cortisol 130ng/dL (reference range <100)
- 24 hour urine cortisol 77 (reference range 3.5 – 45)
- Plan: discontinue COC and repeat testing with overnight Dex included in 3 months

Testing after holding COC for 3 months

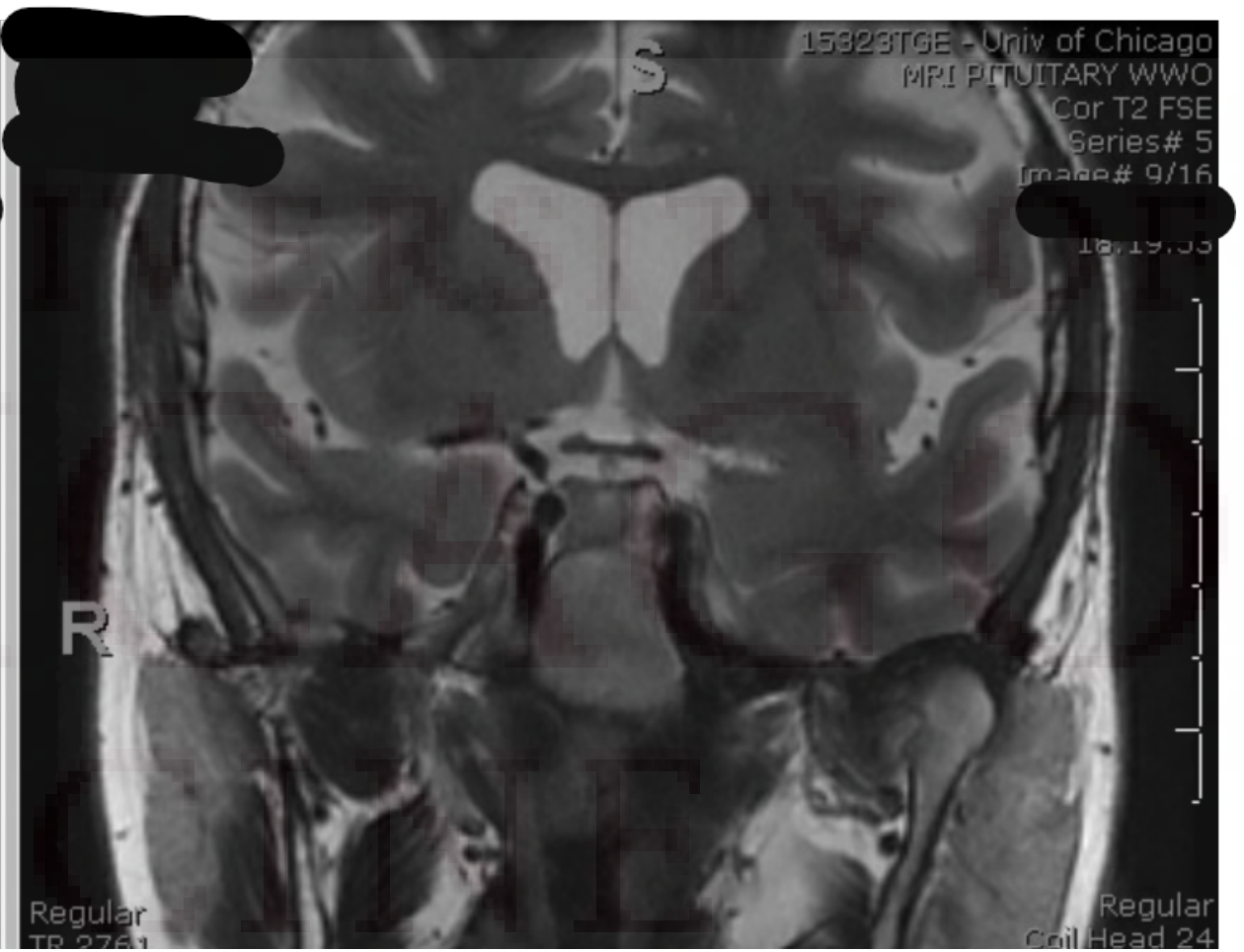
	6/2/16 0911	12/1/16 1459	12/5/16 1200	12/6/16 2327	12/9/16 0750
LH		4.6			
FSH		4.5			
Te binding globulin		62			
Total testosterone		23			
Free testosterone		4			
Urine free cortisol (reference range 3.5 – 45)			180		
Saliva cortisol (reference range <100)				191	
Cortisol	32.8				4.7 (after DST)
ACTH	25.8				
Anti Mullerian Hormone		5.4			

Assessment – Cushing's disease

- Patient has a history of primary amenorrhea with high cortisol levels found incidentally on an ACTH stimulation test performed to rule out nonclassical CAH.
- UFC and midnight salivary cortisol are high. AM cortisol level was not suppressed after 1 mg dose of dexamethasone
- ACTH level was in the low normal range but not suppressed and a prior CT of abdomen does not reveal an adrenal lesion or other adrenal abnormalities -> suspicion for Cushing's disease

Next steps?

Pituitary MRI



IMPRESSION: Negative MRI of the brain and sella including gadolinium enhancement. There is no discrete mass to confirm the presence of a pituitary microadenoma.

Next step?

Pituitary clinic at USC

- 2/2017
  - Tesla 7 MRI done and was able to visualize a 3 mm tumor on the right
  - IPSS done, tumor localized on the right side
- 7/2017
  - Patient underwent TSS at USC
  - Pathology positive for neuroendocrine cells staining for ACTH

Post-op course

- Postop day 3, her cortisol nadir was 1.6 and she was placed on hydrocortisone 20 mg in AM and 10 mg at 4 pm.
- She had transient DI followed by SIADH.
- Free T4 and prolactin were normal postop

- No consensus on the criteria for remission after resecting an ACTH-producing tumor
  - Remission is generally defined as morning serum cortisol values 5 g/dL (138 nmol/L) or UFC 28 –56 nmol/d (10 –20 g/d) within 7 days of selective tumor resection (Nieman et al, JCEM 2015, 100(8):2807–2831)
- Endo Society guidelines 2015
  - Recommend measuring serum sodium several times during the first 5–14 days after transsphenoidal surgery
  - Recommend assessing free T4 and prolactin within 1–2 weeks of surgery, to evaluate for overt hypopituitarism
  - Recommend obtaining a postoperative pituitary MRI scan within 1–3 months of successful TSS (Nieman et al, JCEM 2015, 100(8):2807–2831)

Follow up endo visit

- 8/2017 endo clinic visit
  - Has not had a menstrual cycle yet
  - Sodium levels have normalized
  - Was still on hydrocortisone 20mg in AM and 10mg at 4pm
  - Labs after holding hydrocortisone for 24 hours:
    - 8AM cortisol 11.8
    - ACTH 20.7

Next steps?

Follow up

- Menstrual cycles resumed 2-3 month after surgery, were regular every 4 weeks
- Lost ~15-20 pounds since surgery
- Repeat MRI at USC was normal
- Patient had repeat lab testing

12/4/17 labs:
Cortisol 6.5
24 hour urine cortisol 22 (reference range 3.5 – 45)
DHEA-S 270.6 (reference range 98.8-340)

7/2/18 labs:
DHEA-S 230.7 (reference range 98.8-340)
MN Saliva cortisol 160ng/dL (reference range <100) → Bad sample, was repeated
24 hour urine cortisol 27 (reference range 3.5 – 45)
IGF-1 157 (reference range 66 – 303)
Free T4 1.18

5/2019 After DST, AM cortisol 1.5

↓

MN Saliva cortisol <50ng/dL

Long term follow up

- Monitoring should include checking late-night salivary cortisol, a 24-hour urinary cortisol, and/or DST, using the same criteria as for diagnosis
- Consider reevaluation at any time if they experience a return of their initial symptoms

Geer et al. Pituitary (2017) 20:422–429

Table 1 Follow-up intervals in Cushing's disease patients after pituitary surgery

		In a patient with:	Currently not on steroid replacement and not on drug therapy for Cushing's disease		Currently on exogenous glucocorticoid supplementation		Currently on drug therapy for Cushing's disease[a]	
			Current biochemical hypercortisolism[b]		Current biochemical adrenal status		Current biochemical hypercortisolism[b]	
			a. Absent[c]	b. Present[d]	c. Low[e]	d. Normal[f]	e. Absent[c]	f. Present[d]
Following pituitary surgery	(i) 1–3 months after surgery	A. No symptoms	*4*	*4*	*6*	*4*	*4–6*	*2–4*
		B. Symptoms of adrenal insufficiency currently[g]	*4–6*		*4*	*4*	*4*	
		C. Symptoms of Cushing's Disease currently[h]	*4*	*4*	*6*	*4*	*4–6*	*4*
	(ii) 3–12 months after surgery	A. No symptoms	*12* (*8–26*)	*4*	*8–10*	*4–6*	*6*	*4*
		B. Symptoms of adrenal insufficiency currently[g]	*4*		*4*	*4*	*4*	
		C. Symptoms of Cushing's Disease currently[h]	*4*	*4*	*6*	*4*	*6–8*	*4*
	(iii) Beyond 12 months after surgery	A. No symptoms	*24*	*4*	*6–8*	*6*	*12*	*3–4*
		B. Symptoms of adrenal insufficiency currently[g]	*4*		*4*	*4*	*4*	
		C. Symptoms of Cushing's Disease currently[h]	*4* (*4–8*)	*4*	*6*	*4*	*8* (*8–12*)	*4*

Notes empty solid grey cells indicate deleted scenarios, which the panel decided were implausible

This table refers to patients with Cushing's disease who have had pituitary surgery (white cells indicate agreement; grey cells indicate disagreement). In each cell, the value in bold is the median panel response (i.e., median follow-up recommendation in weeks); values in parenthesis are the range of panel response values

Long term remission

The Postoperative Basal Cortisol and CRH Tests for Prediction of Long-Term Remission from Cushing's Disease after Transsphenoidal Surgery

John R. Lindsay, Edward H. Oldfield, Constantine A. Stratakis, and Lynnette K. Nieman

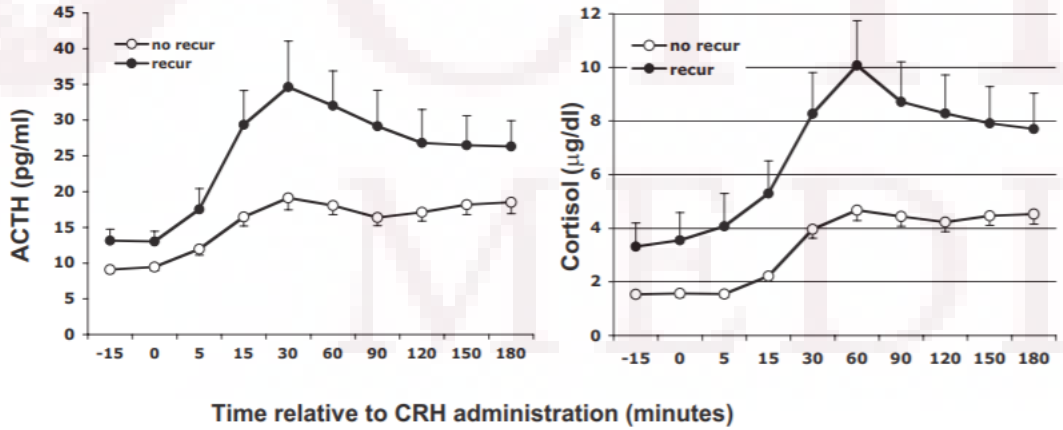


FIG. 3. Postoperative plasma ACTH and serum cortisol responses to CRH stimulation testing (1 μg/kg iv) 4–24 d after surgery at 0800 and/or 2000 h, according to long-term follow-up remission status (●, recurrence; ○, remission). Values are mean ± SEM. (To convert ACTH to picomoles per liter, multiply by 0.22; to convert cortisol to nanomoles per liter, multiply by 27.6.)

- Subjects were CD patients with initial remission after adenomectomy or hemihypophysectomy (n = 14)
- Followed for 11 years
- Study found postoperative cortisol below 2 ug/dl predicts long-term remission after transsphenoidal surgery in CD

TABLE 1. Relationship between nadir postoperative serum cortisol values on d 3-5 after TSS and long-term remission

Serum cortisol (μg/dl)	Remission status +	Remission status −	Total
<2	267	28	295
2–4.9	24	6	30
Total	291	34	325

Lindsay et al. July 2011, 96(7):2057–2064

Long term remission

Dynamics of postoperative serum cortisol after transsphenoidal surgery for Cushing's disease: implications for immediate reoperation and remission

Marc Mayberg, MD,[4] Stephen Reintjes, MD,[3] Anika Patel, BS,[1] Kelley Moloney, ARNP,[1] Jennifer Mercado, ARNP,[1] Alex Carlson, BA,[2] James Scanlan, PhD,[2] and Frances Broyles, MD[1]

[1]Swedish Pituitary Center, Swedish Neuroscience Institute; [2]Swedish Center for Research and Innovation; and [4]Department of Neurological Surgery, University of Washington, Seattle, Washington; and [3]Department of Neurological Surgery, University of South Florida, Tampa, Florida

- Studied 89 patients with CD
- Measured serum cortisol levels every 6 hours for 72 hours
- Found cortisol level of 2.1 µg/ dl at any point was an accurate predictor of 6-month remission

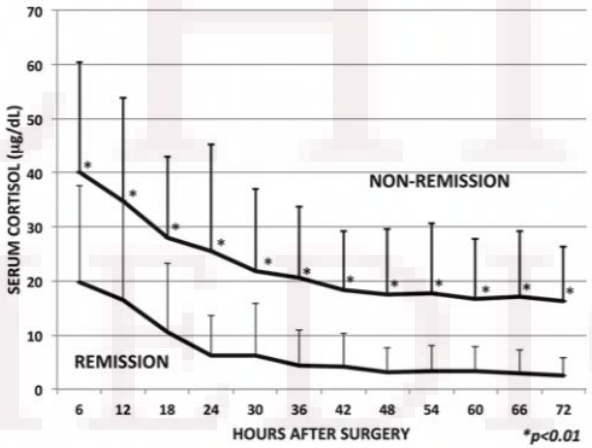
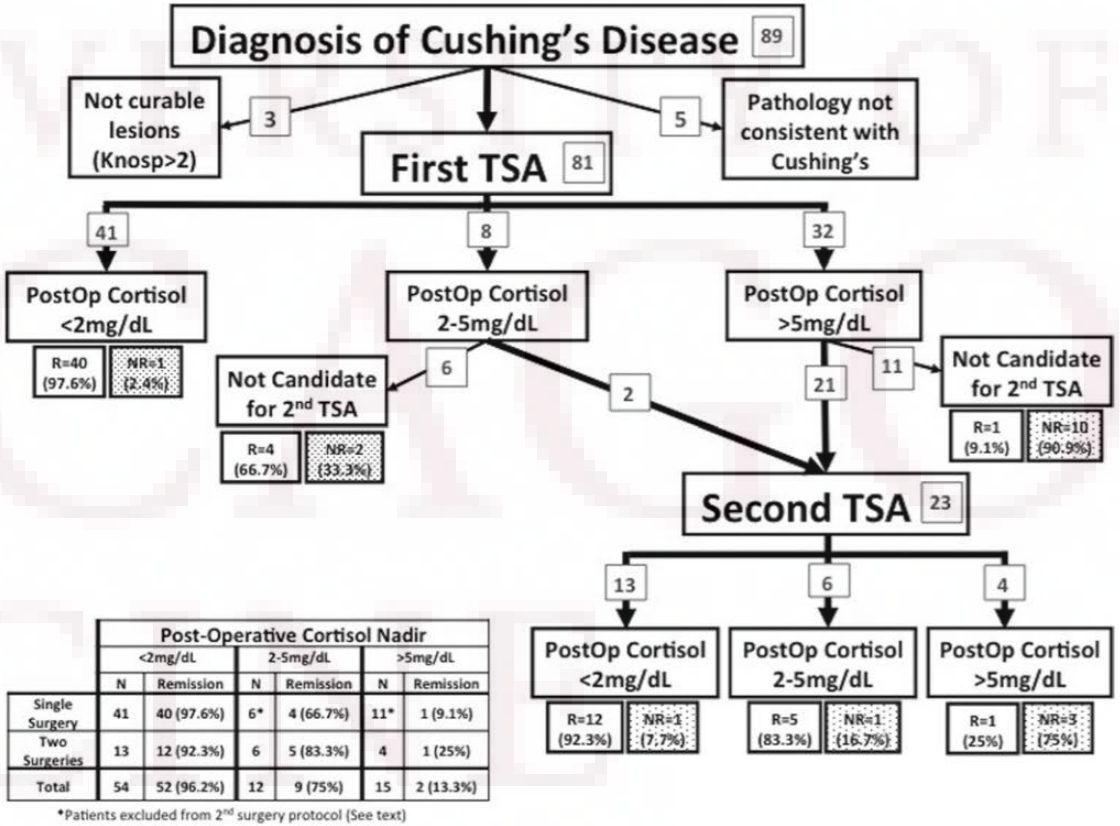


FIG. 3. Mean serum cortisol measurements at 6-hour intervals after surgery for CD for patients achieving remission (*lower line*) versus those without remission (*upper line*). Values are expressed as means ± SDs. There were significant differences in cortisol levels between groups at each time interval ($p < 0.01$).



	Post-Operative Cortisol Nadir					
	<2mg/dL		2-5mg/dL		>5mg/dL	
	N	Remission	N	Remission	N	Remission
Single Surgery	41	40 (97.6%)	6*	4 (66.7%)	11*	1 (9.1%)
Two Surgeries	13	12 (92.3%)	6	5 (83.3%)	4	1 (25%)
Total	54	52 (96.2%)	12	9 (75%)	15	2 (13.3%)

*Patients excluded from 2nd surgery protocol (See text)

FIG. 2. Schematic diagram showing distribution and remission rates of subgroups based on postoperative cortisol measurements and immediate second surgery (see text for details). Calculations of rates for remission (R, *white box*) and nonremission (NR, *hatched box*) are shown below each subgroup.

Mayberg et al. J Neurosurg 129:1268–1277, 2018

Recurrence

- Reported recurrence rates range from 3 to 47 % (mean time to recurrence 16–49 months)
- Patients need lifelong monitoring and follow up

Ayala et al., J Neurooncol. 2014; 119(2): 235–242

Menstrual Abnormalities in Cushing's Disease

Menstrual Abnormalities in Women with Cushing's Disease Are Correlated with Hypercortisolemia Rather Than Raised Circulating Androgen Levels

J. LADO-ABEAL, J. RODRIGUEZ-ARNAO, J. D. C. NEWELL-PRICE, L. A. PERRY, A. B. GROSSMAN, G. M. BESSER, AND P. J. TRAINER,

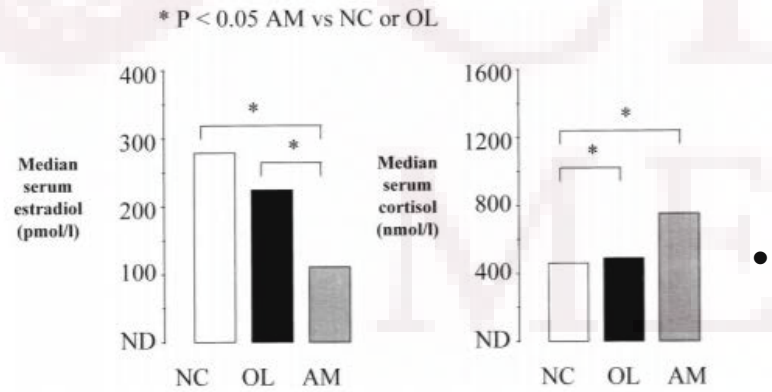


FIG. 1. Comparison between median serum levels of E_2 (*left*) and median serum cortisol levels (*right*) in females with Cushing's disease and NC, OL, or AM.

- 45 patients subdivided into 4 groups
  - normal cycles (NC; 26–30 days)
  - oligomenorrhea (OL; 31–120 days)
  - amenorrhea (AM; >120 days)
  - polymenorrhea (PM; <26 days)
- 80% of patients with Cushing's syndrome had menstrual irregularity, and this was most closely related to serum cortisol rather than to circulating androgens

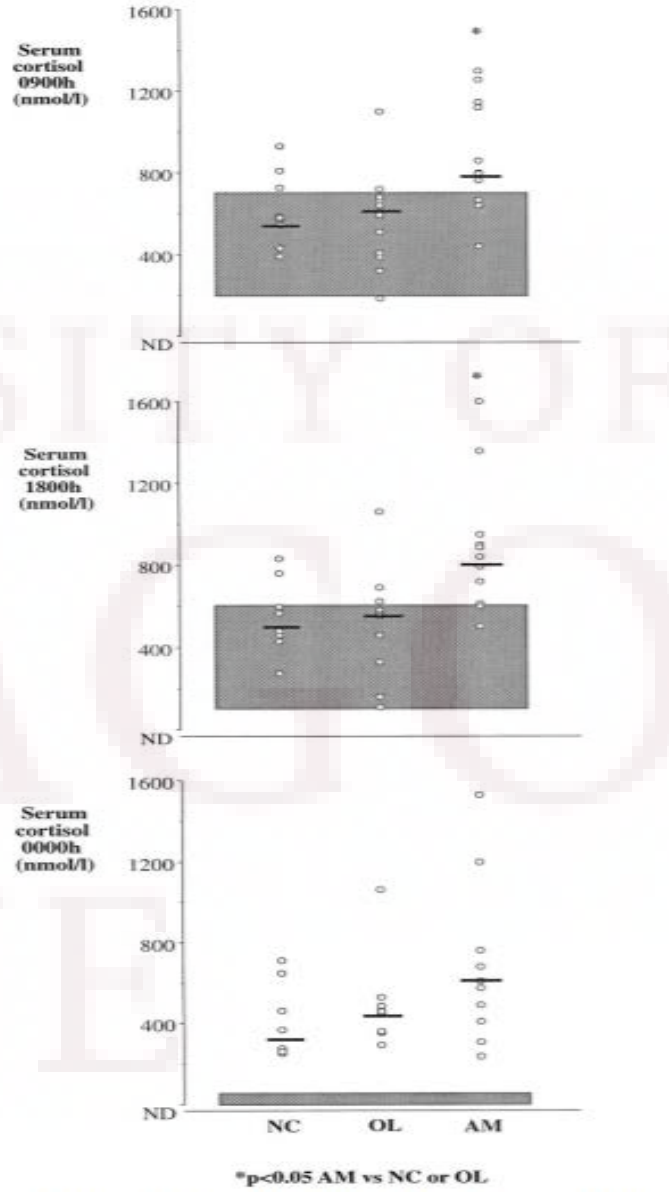


FIG. 2. Serum cortisol levels at 0900, 1800, and 2400 h in women with Cushing's disease and NC, OL, and AM. The *black line* represents the median, and the *shadowed area* shows the normal range.

Objectives

- Discuss causes of primary amenorrhea
- Discuss causes of elevated DHEA-S level
- Discuss clinical management and follow up of Cushing's disease

References

- Ayala et al. Detection of recurrent Cushing's disease: proposal for standardized patient monitoring following transsphenoidal surgery. J Neurooncol. 2014; 119(2): 235–242.
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