28 YO M WITH PARANOID AND RELIGIOUS DELUSIONS

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Endorama
January 4, 2018

March 2017: 28 yo M brought to the ED by his family with paranoid and religious delusions

- Evening prior to admission, accused friend of spying on him and collecting information about him from family members
- On return home, told girlfriend that someone was trying to murder him and displayed paranoid behavior, staying up most of the night, fearful of being shot and concerned about bombs in the home.
- The following morning, he told parents that his brother was dead and that his sister was dead in the basement (patient does not have a sister).

Additional history:

- Reports increased occupational stress and concerns about a possible STI. Also notes that he went to a cigar shop prior to dinner but cannot recall what transpired there.
- Poor historian, reticent; family reports hx of major depression and anorexia (both in remission), alcoholism.
- When queried about his strange behavior:
  - “I came to a point where I work too hard and I started to sound loony”

ROS

Constitutional: No change in appetite, no night sweats, fevers
Vision: No photophobia, blurred vision, or other visual changes
ENT: No difficulty swallowing, sinus congestion, hearing deficits
CV: No palpitations, chest pain, lower extremity edema.
Pulm: No dyspnea, wheezing, cough
GI: No abdominal pain, nausea, vomiting, diarrhea.
GU: **+urinary frequency.** No dysuria, hematuria, discharge
ENDO: No heat or cold intolerance, glucose intolerance, **+polyuria**
MSK: No myalgias, joint swelling, abnormal gait.
Neuro: No weakness, tremor, HA, numbness, paresthesias
Skin: No rashes, hyper/hypopigmentation.
Psych: Stress, **A/V hallucinations+, paranoia+, no SI/HI.**

Past Medical History

- **PMH**
  - Alcohol abuse
    - Binge drinking (2008-2016)
    - Occasional social drinker now
  - Anorexia
  - Major Depression
  - HTN
- **PSH**
  - Tonsillectomy
- **Social Hx**
  - Pipe smoking
  - No other drugs
  - Computer Technician
- **Medications**
  - 5-hydroxytryptophan supplements
  - *MVI*
- **Allergies**: NKDA
- **Family Hx**
  - Father – Diabetes, HTN
  - Mother – Diabetes, CAD, Depression, Bipolar?
  - Brother – Healthy
  - No pituitary tumors, endocrinopathies, osteoporosis

Physical Exam in clinic

Vitals: T 36.6 °C, BP 153/94, HR 62, SpO2 97% RA, Wt 83.5 kg (184 lbs), Ht 178 cm (5’10”), BMI 26.4 kg/m^2

Gen: Pleasant gentleman, no apparent distress. Appears comfortable.

HEENT: NC/AT, PERRL, EOMI, No oral lesions, MMM. **Moon facies.**

Neck: No cervical LAD, supple.

CV: Normal rate, regular rhythm, no murmurs, no LE edema

Pulm/Chest: Clear bilaterally, no rales, wheezes.

GI: Normal BS, non-distended, soft, non-tender, no rebound, no guarding.

MSK: No proximal muscle weakness. Normal tone.

Neuro: AOx3, CN II-XII intact, no focal deficits. Normal strength throughout and normal reflexes. **+Gait ataxia**

Skin: No rashes or ulcers.

Psych: Inappropriate, flat affect, bizarre behavior, no SI/HI

What is your differential diagnosis?

Infection
Metabolic
- Primary (e.g. porphyria)
- Hepatic
- Renal

Primary psychiatric disorder
- Schizophrenia
- Bipolar
- Major Depression

Endocrine

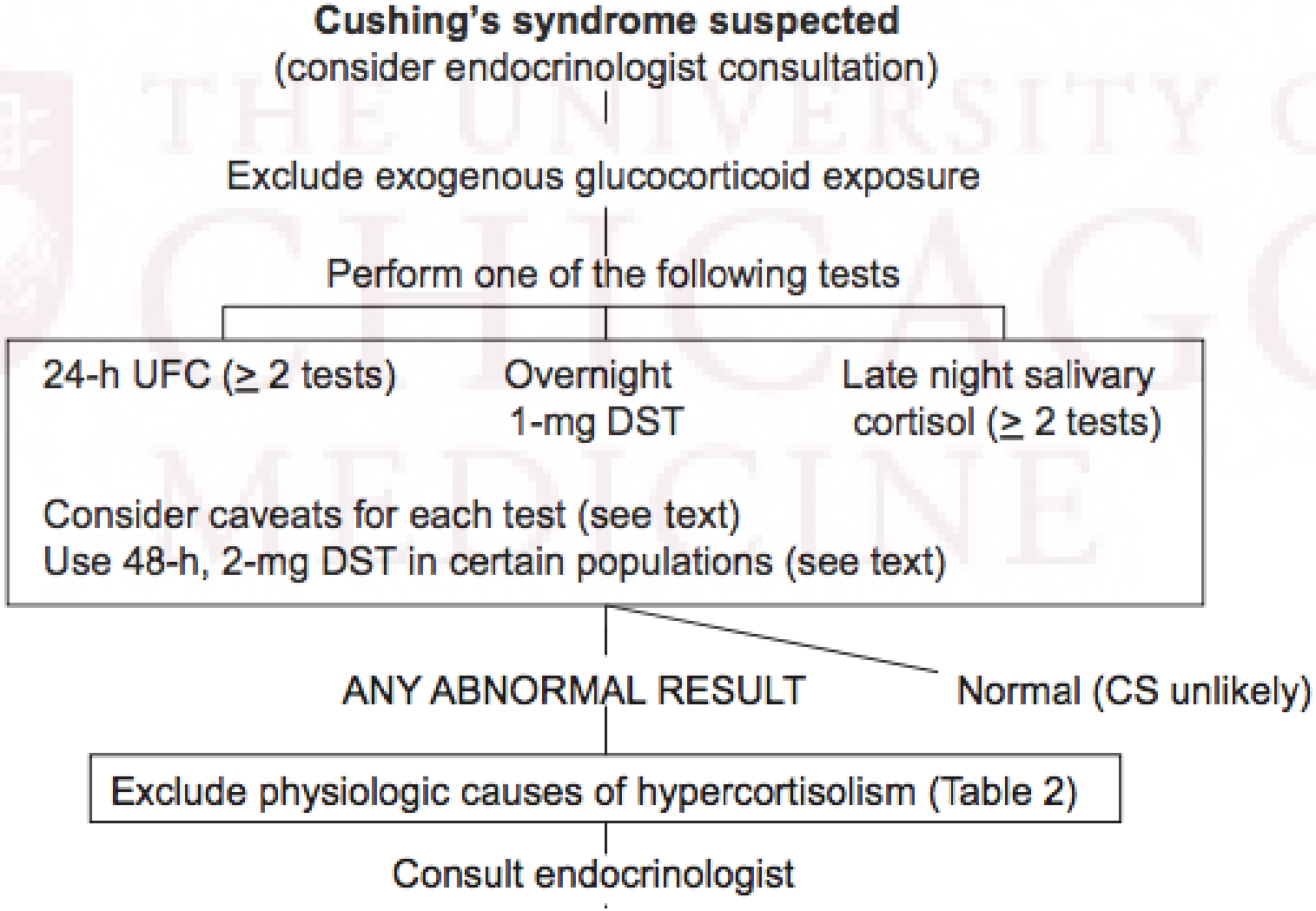
Paraneoplastic/Inflammatory
Medication/drug-related

What Endocrine specific issues are you concerned about?

- Thyroid: Thyrotoxicosis
- Parathyroid : Hypercalcemia
- Adrenal disease:
  - Hypercortisolism
  - AI (hyponatremia)

Would you screen for Cushing's at this point?
If so, what test(s) would you like?

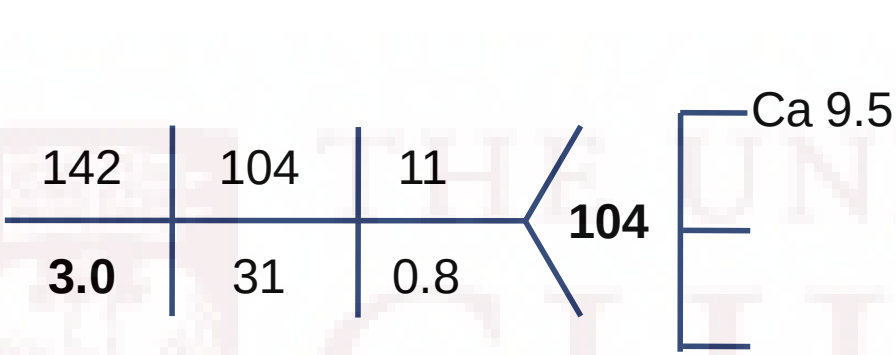
Endocrine Society guidelines recommend:

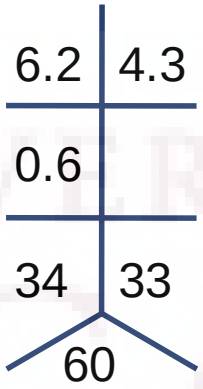


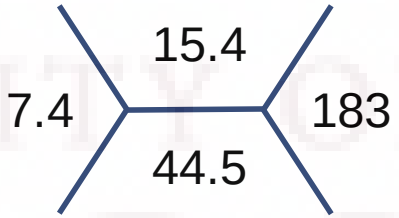
Screening Tests for Cushing's

1. **24h Urine free Cortisol**
   i. Avoid if GFR <60, >5L fluid intake
2. **Overnight 1mg DST**
   i. Positive if 8 AM cortisol <1.8
   ii. Caveats:
      i. Estrogen can lead to false positives (up to 50%) via induction of SHBG, CBG; Stop x6 weeks prior to testing
      ii. Hypoalbumin, illness, nephrotic syndrome --> false negative
      iii. CYP3A4 inducers (anti-epileptics) increase Dex metabolism --> false neg
3. **Late night Salivary Cortisol**
   i. Use in MILD Cushing's
   ii. BEST screening test (high sens/spec) because it is NOT elevated in depressed or obese patients
   iii. 2-3 consecutive nights collection increases accuracy

Admission labs and studies







TSH 0.7 (0.27 – 4.2 mIU/mL)
Free T4 1.05 (0.55 -1.60 ng/dL)
Free T3 3.45 (2.53 – 4.34 pg/mL)

CT Head: No intracranial hemmorhage, mass, hydrocephalus or edema. No calvarial fractures.
EKG: normal
Blood cultures: pending

Other labs:
Lactate 1.08
Lipase 62
CK 173
Acetaminophen: Undetectable
Salicylate: Undetectable
EtOH: Undetectable
Utox: Negative
UA: Bland

Neurology consult obtained

Recommended additional testing:

- Lyme Ab, West Nile, HSV, Syphilis, HIV
- ANA, RF, CRP
- B12, Folate
- LP with gram stain, glucose and protein, infectious studies
- EEG
- MRI
- **Evaluation for Cushing's**

Neurology consult cont…

Recommended additional testing:

- Lyme Ab, West Nile, HSV, Syphilis, HIV - **negative**
- ANA, RF, CRP - **normal**
- B12 - **normal**, Folate - **low**
- LP: gram stain negative, glucose and protein normal, infectious studies **unremarkable**
- EEG: **non-diagnostic**
- MRI: ***Abnormal symmetric hyperintense signal within the pons with few small foci of scattered white matter signal. Differential diagnosis includes MS, vasculitis, Lyme disease, sarcoid, central pontine myelolysis,/osmotic demyelination syndrome, chronic ischemia, or other white matter disorder. NO evidence of abnormal enhancement.***

Psychiatric Symptoms associated with Cushing's

- Depression of any kind 50-70% of cases
- Atypical Depression – present in 50% of patients with CS
  - Associated with decreased CRH secretion
  - Irritability
  - Hyperphagia
  - Hypersomnia
  - Increased Fatigue

TABLE 1 | Prevalence of major depression in patients with active CS (adapted from Sonino and Fava, 2001).

References	Diagnosis	No. of PTS	Major depression: No. of PTS (%)
Sonino et al., 1998	CD	162	88 (54)
Haskett, 1985	All forms	30	24 (80)
Hudson et al., 1987	CD	16	9 (56)
Loosen et al., 1992	CD	20	13 (65)
Sonino et al., 1993	CS excluding CD	20	10 (50)
Kelly, 1996	All forms	209	120 (57)
Dorn et al., 1995	All forms	33	17 (51)
Total		490	281 (57)

Pivenllo wt al. Front. Neurosci. 9:129. 2015

Minimal evidence regarding psychosis…

Starr AM: Personality changes in Cushing's syndrome. J Clin Endocrinol Metab 1952;12: 502–505.

- 53 patients with Cushing's Disease
- 35% had marked personality alterations
- 25% showed frank psychosis which resulted in institutionalization

Inpatient Cushing's evaluation

Serum Cortisol: 23 (6.7 – 22.6 ug/dL) ?8AM

Late night salivary cortisol: 1.431 ug/dL >12x ULN
(<0.112 ug/dL)

24 Urine Cortisol: 2964 >7x ULN
(58-403 ug/24h)
Urine volume: 3900 mL

Discharged with referrals to Endocrinology and Psychiatry

July 2017: Patient update

- Presents to ED with back pain
- Reports multiple falls at home
- Exam:
  - BP 141/97, P 105
  - Neurovascularly intact with 5/5 strength and sensation intact in bilateral UE, LE
  - No evidence of cord compression – no changes in bowel/bladder habits, no saddle anesthesia
  - However, muscle wasting noted in discharge summary
- Xray L-spine:
  - Multilevel inferior thoracic and lumbar compression fractures of indeterminate age at T9, T10, T11, T12, L1, L3, L5
- Discharged from ED with Naproxen and referral to Rheumatology

August 2017: Outpatient Endocrinology

- Bilateral rib pain since early 2017
- Unable to maintain posture due to back pain, epigastric pain which becomes worse with eating
- Weakness in bilateral legs and arms – needs to lift his legs to get into a car
- Non-tender gynecomastia
- 50# weight loss in past 9 months (peak weight 350 in 2009)
- Medications: lisinopril 10, furosemide 40, amlodipine 5, potassium 20 BID
- Adrenal CT, BMD, ACTH, cortisol

Endo evaluation: What would you like to do now?

- Labs
  - ACTH: 64 (7 – 69 pg/mL)
  - Cortisol: 22 (6.7 – 22.6 ug/dL)
- BMD:
  - T-score at L-spine was **-2.7**
  - T-score at hips was 0.0
- Bone scan:
  - Numerous bilateral rib fractures
  - Bilateral Sacral alar uptake pattern highly suggestive of fractures
  - Abnormal uptake in multiple T, L-spine vertebrae
- CT Abd/Pel
  - Questionable mild thickening of the L adrenal, present since 2011, no discreet nodule
  - R +Nephrolithiasis
- Pituitary MRI: not done
- High-dose dexamethasone suppression test: not done

Referred to UCMC Endocrinology / ED due to rapidly progressive decline, continuing falls and fractures

Admitted to UCMC for expedited evaluation s/p fall at outpatient clinic in IN

- Review of findings thus far:
  - Facial plethora
  - Multiple fractures over past 9 months
  - Now with muscle wasting/weakness 50# weight loss over past 9 months
  - HTN on triple therapy
  - Hypokalemia requring K+ supplements
  - **Endocrine labs notable for:**
    - **Serum Cortisol: 23** (6.7 – 22.6 ug/dL)
    - **Late night salivary cortisol: 1.431 ug/dL** (<0.112 ug/dL)
    - **24 Urine Cortisol: 2964** (58-403 ug/24h)

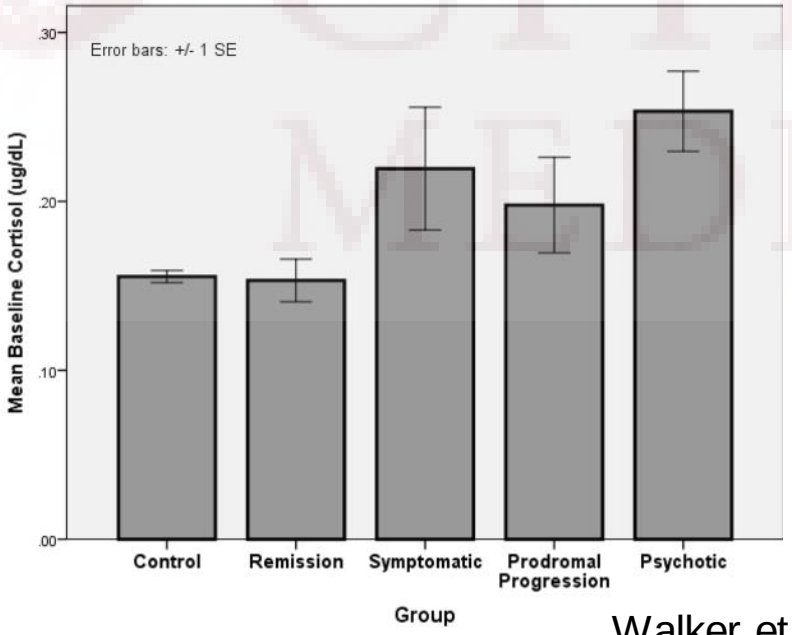
Case closed?

- Seen by inpatient Endocrinology
  - *“Pt with low bone density that could be secondary to rapid weight loss associated with alcoholism; cannot rely on laboratory studies collected during episode of acute psychosis to diagnose Cushing’s syndrome, pseudoCushing’s must be considered…”*

How does acute psychosis affect cortisol levels?

Cortisol Levels and Risk for Psychosis: Initial Findings from the North American Prodrome Longitudinal Study

- Compared cortisol levels in healthy controls with those in individuals who were high risk for psychosis (CHR – clinically high risk)
- Obtained baseline psychiatric assessment, measurement of salivary cortisol of 256 CHR and 141 controls



Higher baseline cortisol in those who became psychotic compared to healthy controls, and compared to CHR subjects who remitted.

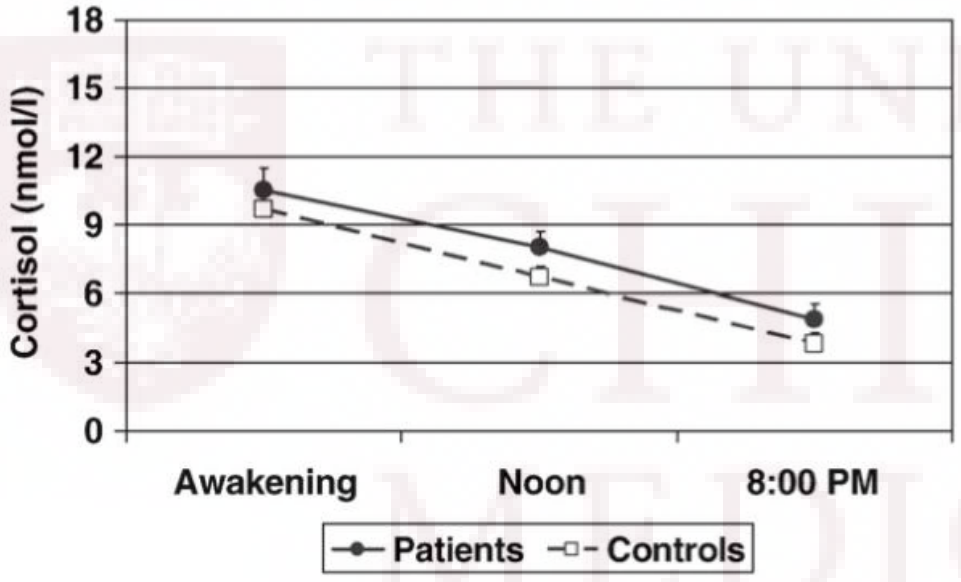
Walker et al. Biol Psychiatry. 2013 Sep 15; 74(6): 410–417.

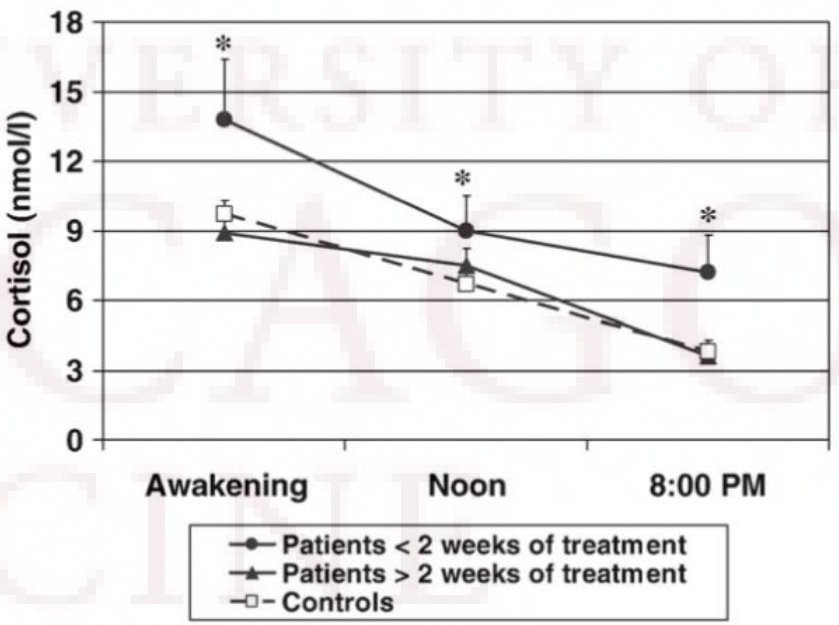
Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: The role of stress and of antipsychotic treatment

- Study characteristics:
- N = 50 subjects, 36 healthy controls
- Subjects aged 18–65 who presented for the first time for a functional psychotic illness
- Patients were further divided into those with less than two weeks (*n*=17) and those with more than two weeks (*n*=33) of antipsychotic drug treatment
- Assessment:
  - Validated psychiatry questionaires
  - Salivary cortisol collected at: 0, 15, 30 and 60 min after awakening,12 pm and at 8 pm
    - Analysis based on AUC of total day using time 0 (awakening), 12pm and 8pm values

Mondelli et al. Schizophr Res. 2010 Feb; 116(2-3): 234–242

Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: The role of stress and of antipsychotic treatment





First-episode psychosis patients had a trend toward higher diurnal cortisol levels (p=0.055), driven mostly by those with less than two weeks of antipsychotics who had significantly higher cortisol levels than both patients with more than two weeks of antipsychotics (p=0.005) and controls (p=0.002).

Mondelli et al. Schizophr Res. 2010 Feb; 116(2-3): 234–242

How does acute psychosis affect cortisol levels?

- Some evidence for elevated cortisol during the first episode of psychosis and recent onset psychotic patients
  - *Cortisol elevation due to psychosis not usually to the degree seen in our patient*
- Patients with psychotic symptoms manifest greater elevations in cortisol than patients with other mood disorders
- Cortisol levels correlate with severity ratings of a range of symptoms in psychotic patients
- CHR youth who go on to develop a psychotic disorder show significantly higher cortisol levels in the year preceding onset
- Cushing's specific:
  - Reassessment following treatment leads to improvement in psychiatric symptoms
  - Some patients have residual symptoms long after biochemical cure

Distinguishing Cushing's from Pseudo-Cushing's

- Combined dexamethasone suppression-CRH stimulation test.
  - Dexamethasone Q6 hours for 2 days
  - Positive: Cortisol >1.4 mcg/dL
  - Injection of CRH.
  - Measure cortisol 15-20 minutes after the CRH injection
  - Positive: 30-50% increase in ACTH and increase in cortisol
- UFC x 1-3 collections
  - Positive: >3.5x ULN
  - Inconclusive if between the upper limit of normal and 3.5 times the upper limit of normal
- Diurnal cortisol test – midnight **serum** cortisol
  - Positive >7.5 mcg/dL)

Returning to our patient…

- Seen by inpatient Endocrinology
  - *Pt with low bone density that could be secondary to rapid weight loss associated with alcoholism; cannot rely on laboratory studies collected during episode of acute psychosis to diagnose Cushing's syndrome, pseudoCushing's must be considered…"*
- Labs
  - Random ACTH 81.7, Cortisol 21.5
  - Repeat random ACTH 79.8, Cortisol 18.6
  - Late-night serum cortisol 20.2 (elevated >7.5 OR >15 u/dL per other sources)
  - 24h Urine Cortisol 848 (3.5 - 45); Urine volume 5300mL
    - *Pts with high urine volume >5L can have >60% more cortisol excreted*
  - Dex-suppressed CRH Stimulation

Dex-suppressed CRH stimulation

- **Combined** low-dose dexamethasone suppression test with CRH stimulation

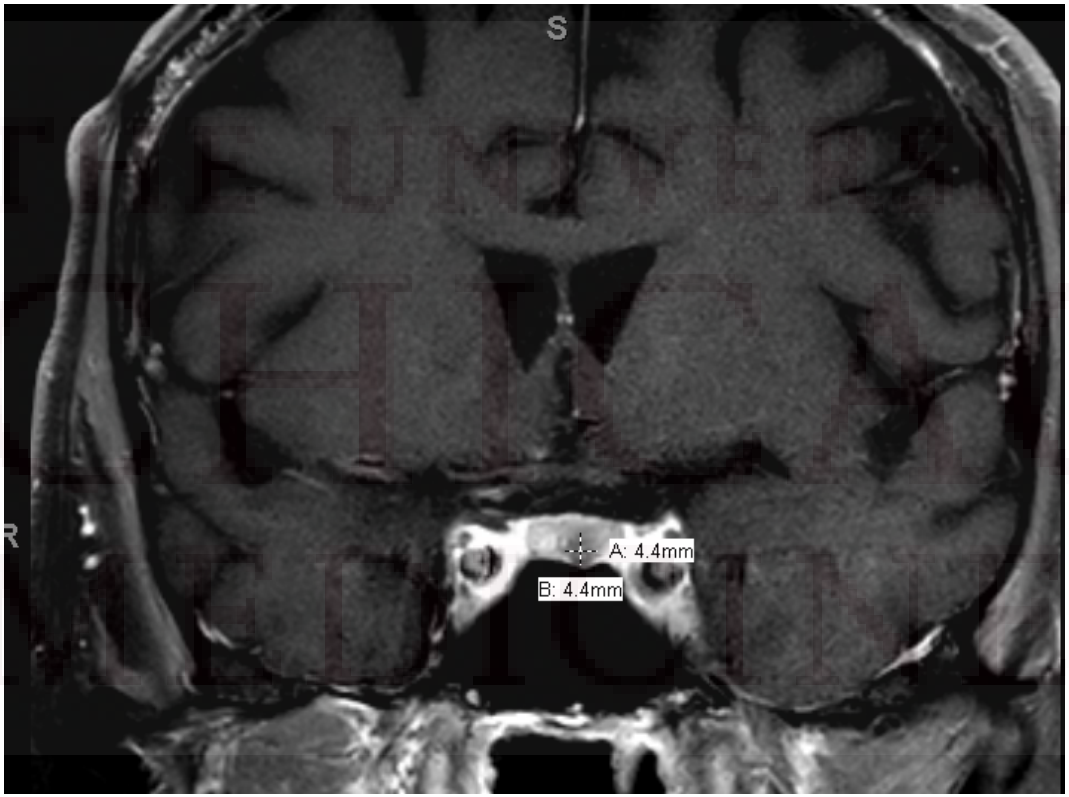
- Dex level: Appropriate **465 ng/dL**
- **Initial studies suggest 15 minute post-stimulation Cortisol >1.4 mcg/dL**
- However, Erickson et al. (n=51 with mild Cushing's) suggest a threshold of Cortisol >2.5 mcg/dL (sens/spec 90%) and ACTH >27 pg/mL

- **LDDST:** AM Cortisol 1.8 – 5 mcg/dL; ACTH < 5 pg/mL; dexamethasone between 200 and 650 ng/dL
- **CRH Stim:** 35% increase in ACTH or 20% increase in Cortisol

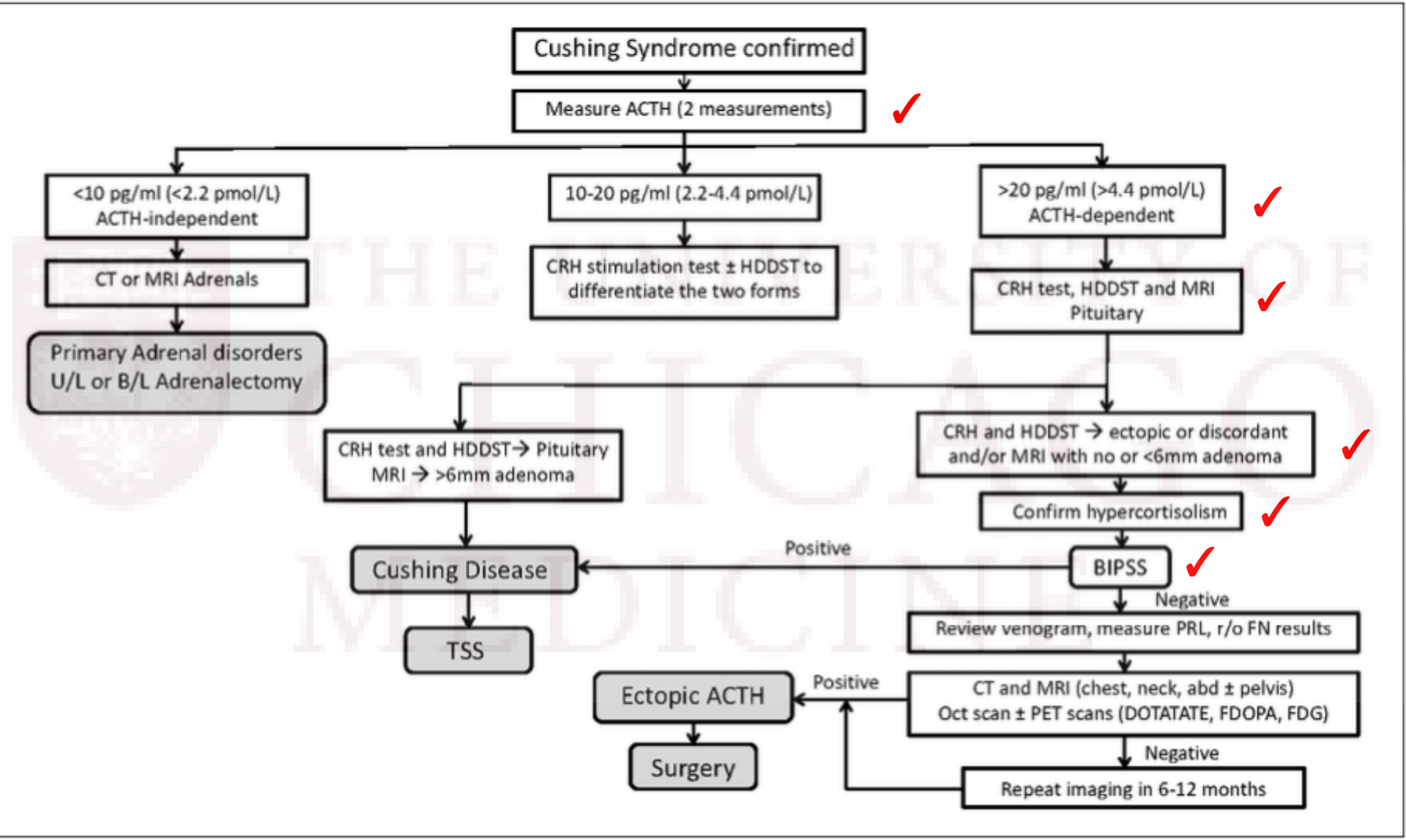
Time	Cortisol (ug/100mL)	ACTH (pg/mL)
-15 min	18.9	29.8
+15 min	**19.2 (1.9 mcg/dL)**	**101.7 (350% incr.)**
+30 min	20.6	87.6
+45 min	20.3	86.8
+60 min	20.9	88.9
+90 min	? 21.5	83.3
+120 min	21.5	82.6
+180 min	22.6	81.1
+240 min	**22.5 (1.2% incr.)**	84.8

Erickson et al. JCEM **92**; 8 2973-2976, 2008.
Yanovski et al. JCEM **83**; 2 348-352, 1998
Uptodate.com

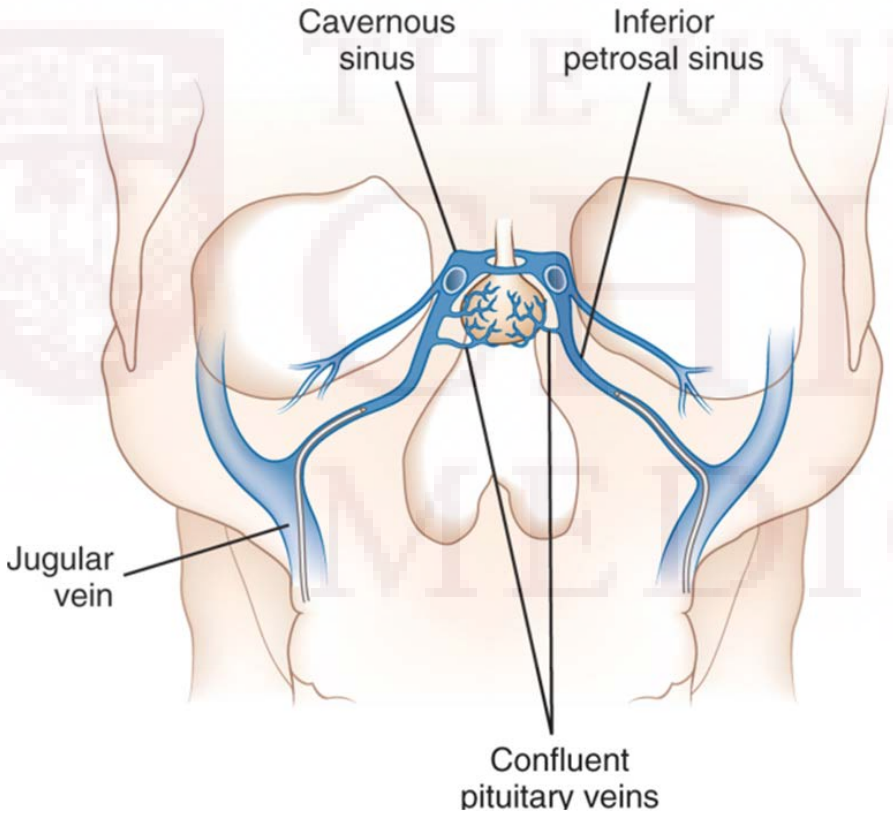
MRI Brain: 4-6 mm pituitary lesion



4 x 6 mm area of oval hypoenhancement in the anterior inferior pituitary gland. Findings could represent a microadenoma in the appropriate clinical setting.

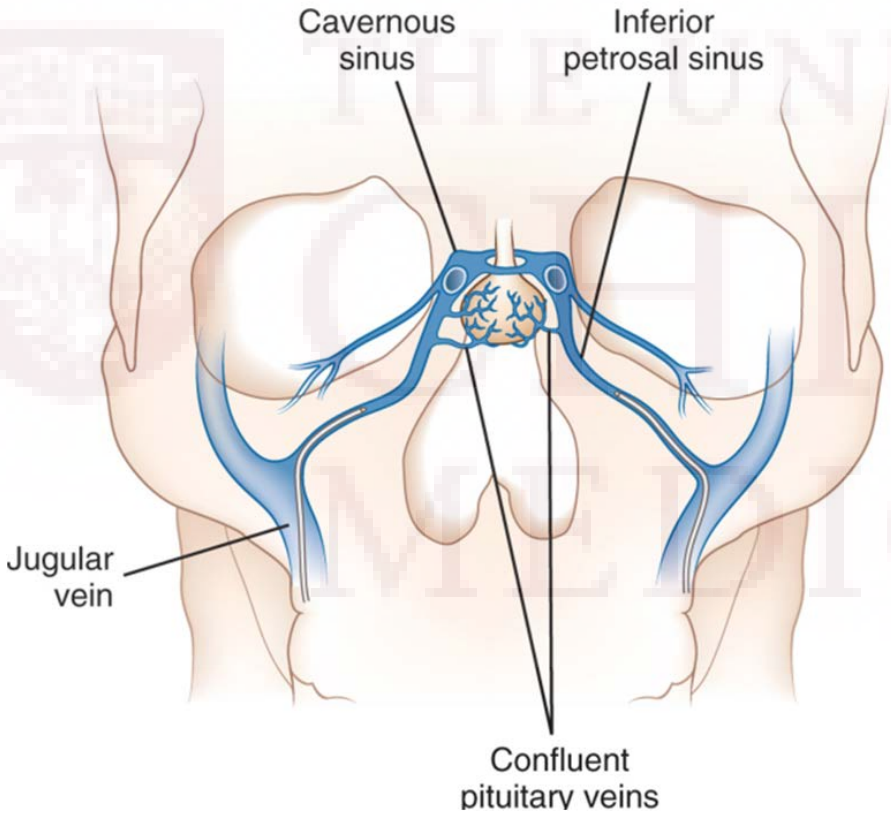

Cushing Syndrome confirmed
Measure ACTH (2 measurements)
<10 pg/ml (<2.2 pmol/L) ACTH-independent
10-20 pg/ml (2.2-4.4 pmol/L)
>20 pg/ml (>4.4 pmol/L) ACTH-dependent
CT or MRI Adrenals
CRH stimulation test ± HDDST to differentiate the two forms
CRH test, HDDST and MRI Pituitary
Primary Adrenal disorders U/L or B/L Adrenalectomy
CRH test and HDDST→ Pituitary MRI → >6mm adenoma
CRH and HDDST → ectopic or discordant and/or MRI with no or <6mm adenoma
Confirm hypercortisolism
Positive
Cushing Disease
BIPSS
Negative
TSS
Review venogram, measure PRL, r/o FN results
Positive
Ectopic ACTH
CT and MRI (chest, neck, abd ± pelvis) Oct scan ± PET scans (DOTATATE, FDOPA, FDG)
Surgery
Negative
Repeat imaging in 6-12 months

Evaluation of Pituitary Cushing's with IPSS



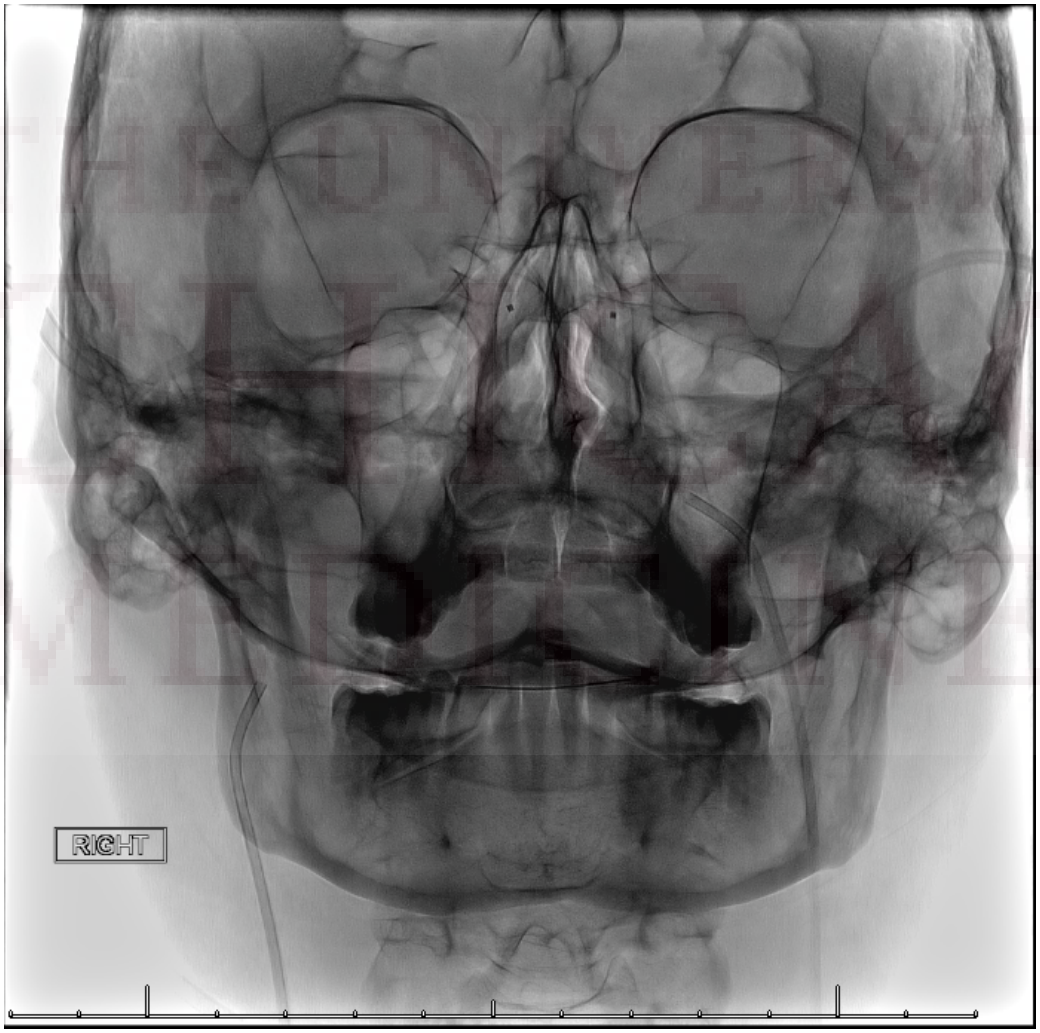
- Pituitary source of ACTH will lead to higher levels of ACTH in the petrosal sinus compared to in a peripheral vein
  - **Normal** individuals will also have an increased Central:Peripheral gradient
  - Test for **localization** only **after** ACTH-dependent hypercortisolism is established, to **rule out** a peripheral source
  - Patient **must be hypercortisolemic at the time** of testing (ensures suppression of normal corticotroph function)
    - MN salivary cortisol the night before
    - 24h Urine cortisol the day prior
    - AM Cortisol the day of procedure

Evaluation of Pituitary Cushing's with IPSS – how the procedure is done



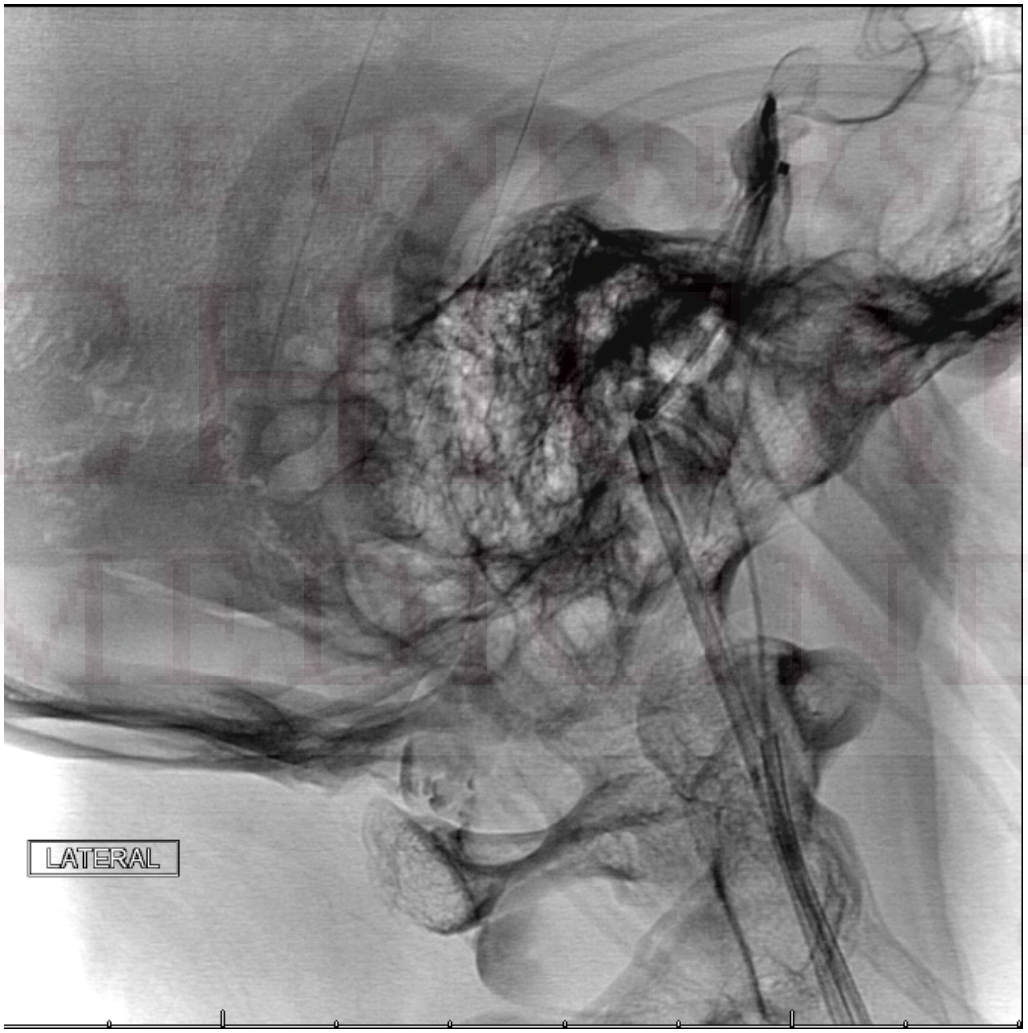
- Performed under fluoroscopy by IR
- Heparin bolus or continuous infusion to reduce risk of VTE
- Bilateral femoral venous sheaths with catheters advanced through the RA to the IJ and up to the petrosal sinus
- Venography to confirm position

IPSS 1



IPSS 2

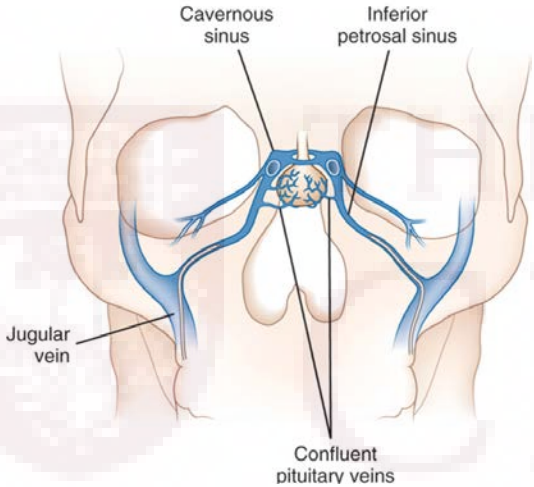
IPSS 3



IPSS 4

IPSS 5

IPSS – Procedure Timeline



Collect simultaneous samples from R, L and peripheral veins:

-5 min

-1 min

0 min: CRH 1 mcg/kg (max 100 mcg) administration

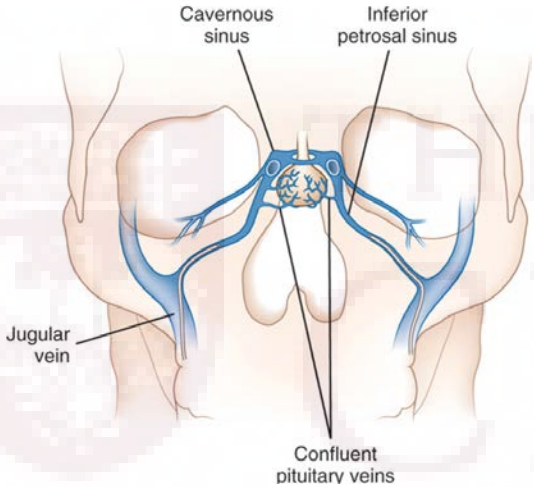
+2 min

+5 min

+10 min

Assay for ACTH, prolactin

IPSS interpretation



- Confirm catheter placement in the petrosal sinus with prolactin
  - Central:Peripheral **Prolactin** Gradient **>1.8**
- Assess for Central Step-up in ACTH
  - **>2X at baseline**
  - **>3X after stimulation with CRH**

Sample report from the lab:

Patient information

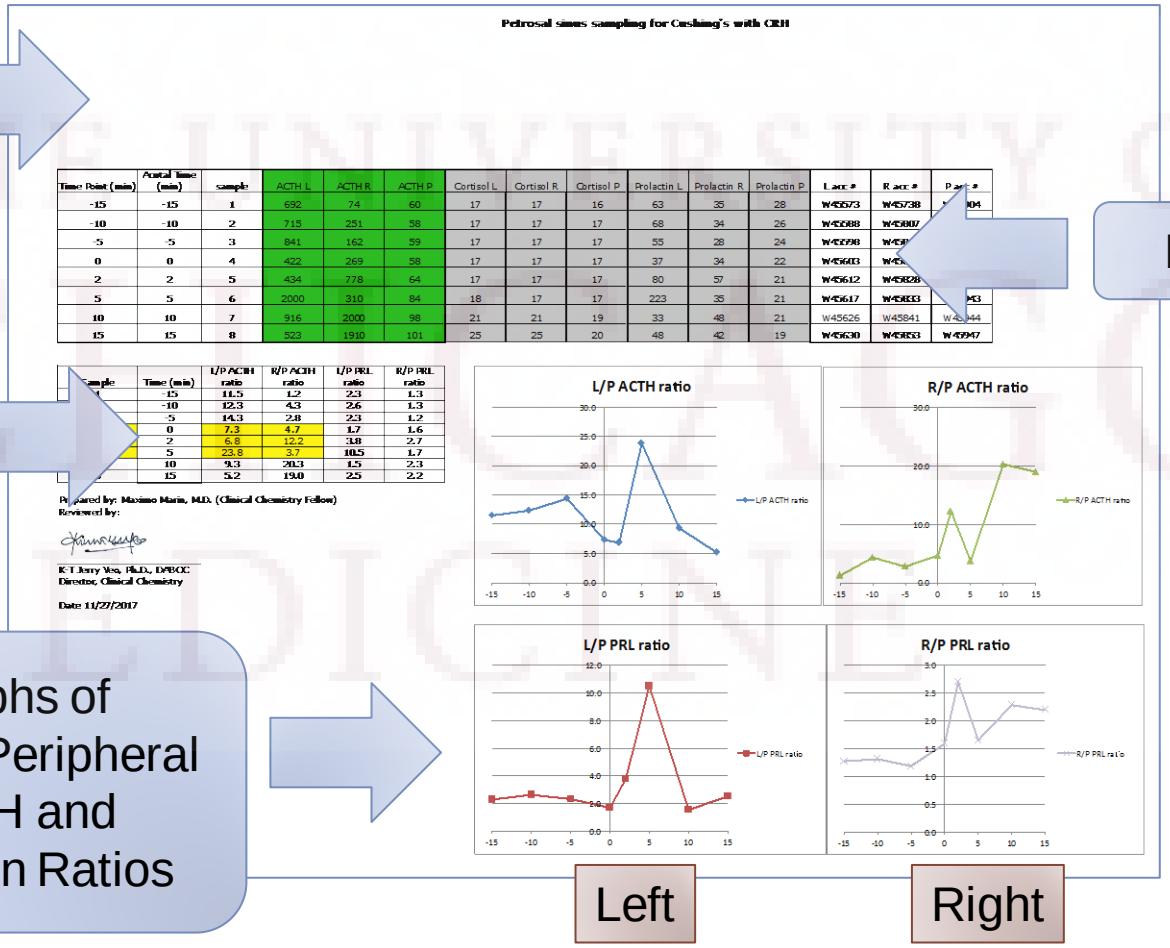
Central:Peripheral ACTH and Prolactin Ratios

Graphs of Central:Peripheral ACTH and Prolactin Ratios

Labs

Left

Right



Petrosal sinus sampling for Cushing's with CRH

Time Point (min)	Actual time (min)	sample	ACTH L	ACTH R	ACTH P	Cortisol L	Cortisol R	Cortisol P	Prolactin L	Prolactin R	Prolactin P	L acc #	R acc #	P acc #
-15	-15	1	692	74	60	17	17	16	63	35	28	W45573	W45738	W45904
-10	-10	2	715	251	58	17	17	17	68	34	26	W45588	W45807	
-5	-5	3	841	162	59	17	17	17	55	28	24	W45598	W45	
0	0	4	422	269	58	17	17	17	37	34	22	W45603	W45	
2	2	5	434	778	64	17	17	17	80	57	21	W45612	W45828	
5	5	6	2000	310	84	18	17	17	223	35	21	W45617	W45833	M3
10	10	7	916	2000	98	21	21	19	33	48	21	W45626	W45841	W45944
15	15	8	523	1910	101	25	25	20	48	42	19	W45630	W45853	W45947

sample	Time (min)	L/P ACTH ratio	R/P ACTH ratio	L/P PRL ratio	R/P PRL ratio
	-15	11.5	1.2	2.3	1.3
	-10	12.3	4.3	2.6	1.3
	-5	14.3	2.8	2.3	1.2
	0	7.3	4.7	1.7	1.6
	2	6.8	12.2	3.8	2.7
	5	23.8	3.7	10.5	1.7
	10	9.3	20.3	1.5	2.3
	15	5.2	19.0	2.5	2.2

Prepared by: Maximo Marin, M.D. (Clinical Chemistry Fellow)
Reviewed by:

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Director, Clinical Chemistry

Date: 11/27/2017

ACTH and Prolactin at all timepoints

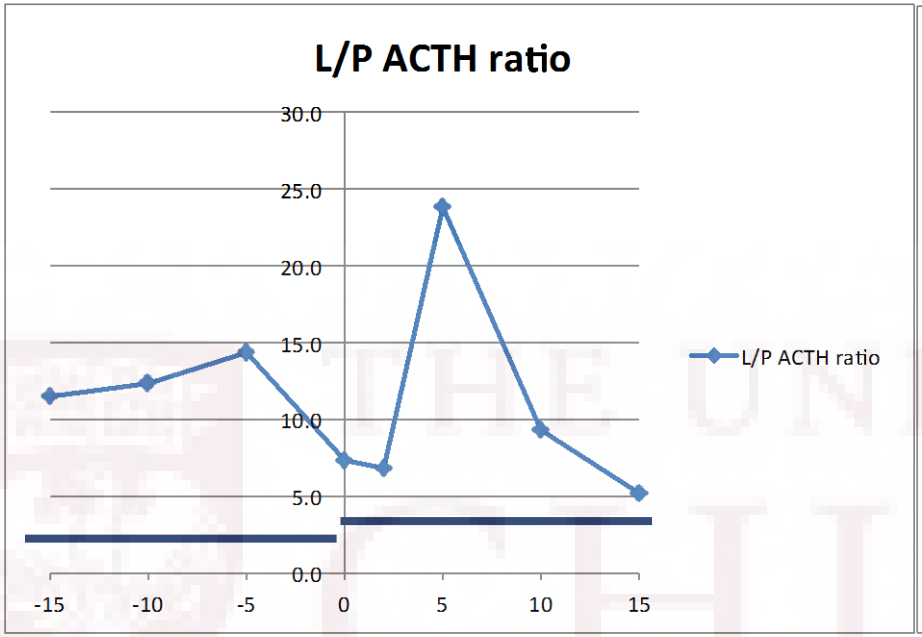
ACTH L	ACTH R	ACTH P	ACTH L	ACTH R	ACTH P	ACTH L	ACTH R	ACTH P
692	74	60	692	74	60	692	74	60
715	251	58	715	251	58	715	251	58
841	162	59	841	162	59	841	162	59
422	269	58	422	269	58	422	269	58
434	778	64	434	778	64	434	778	64
2000	310	84	2000	310	84	2000	310	84
916	2000	98	916	2000	98	916	2000	98
523	1910	101	523	1910	101	523	1910	101

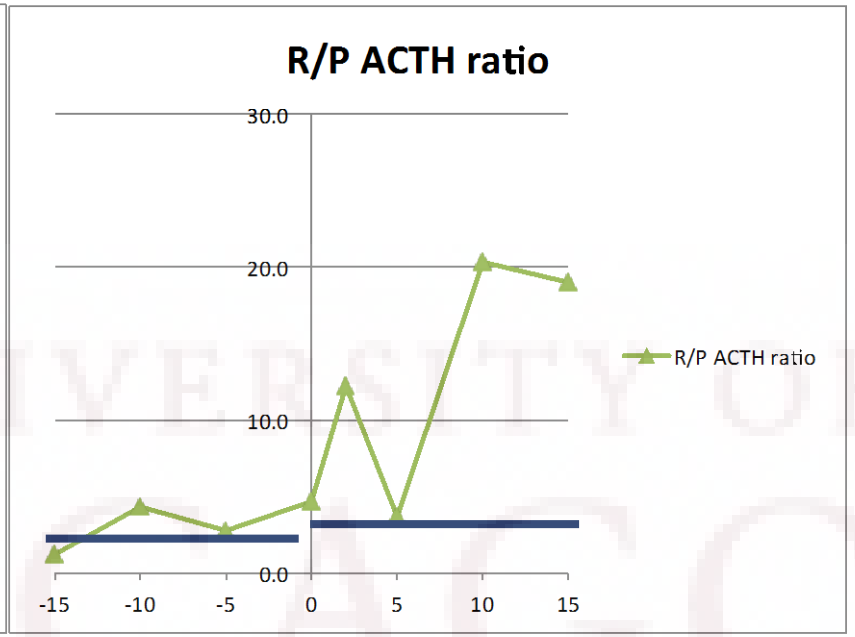
Central:Peripheral ACTH and Prolactin Ratios

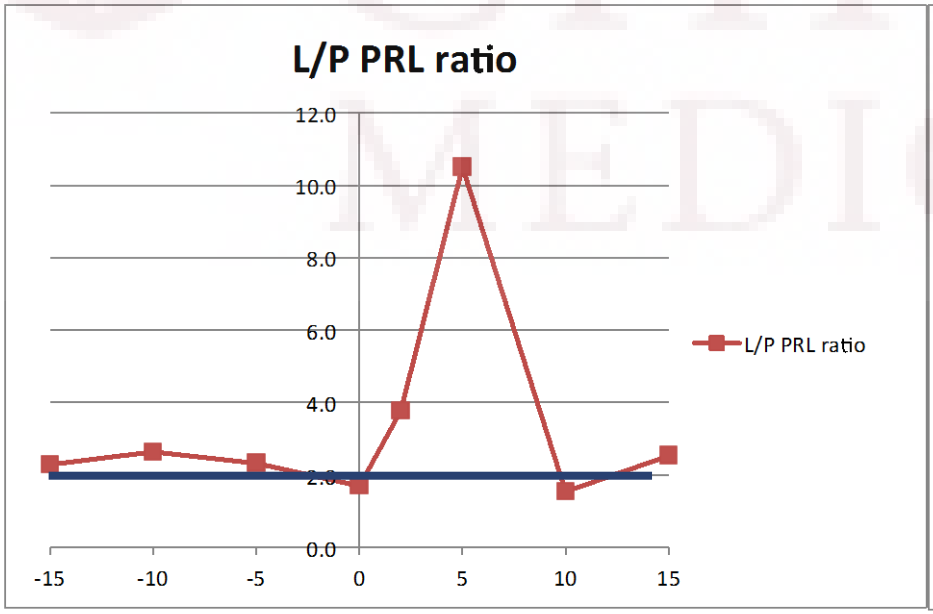
Time (min)	L/P ACTH ratio	R/P ACTH ratio	L/P PRL ratio	R/P PRL ratio
-15	11.5	1.2	2.3	1.3
-10	12.3	4.3	2.6	1.3
-5	14.3	2.8	2.3	1.2
0	**7.3**	**4.7**	1.7	1.6
2	6.8	12.2	3.8	2.7
5	23.8	3.7	10.5	1.7
10	9.3	20.3	1.5	2.3
15	5.2	19.0	2.5	2.2

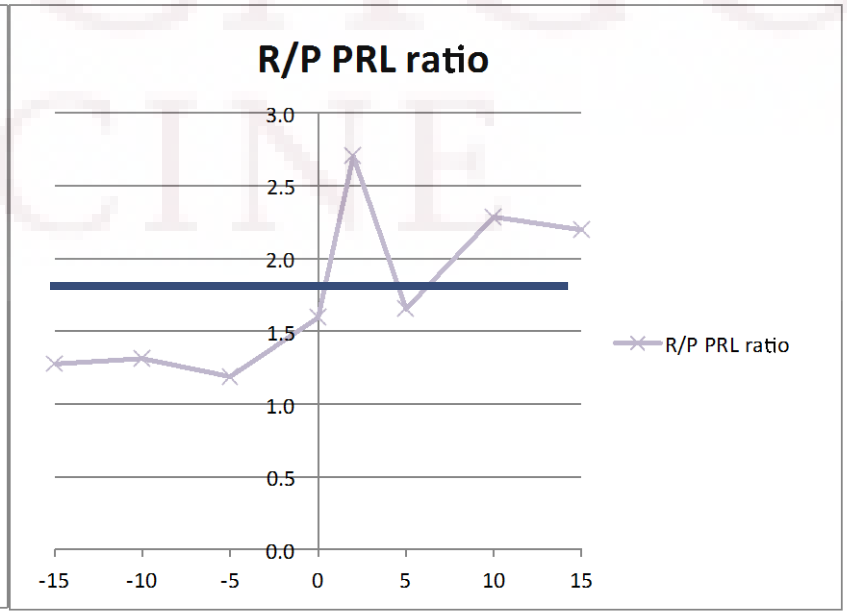
Central:Peripheral ACTH
>2X at baseline
>3X after stimulation with CRH

Central:Peripheral Prolactin >1.8


L/P ACTH ratio
30.0
25.0
20.0
15.0
10.0
5.0
0.0
-15
-10
-5
0
5
10
15
L/P ACTH ratio


R/P ACTH ratio
30.0
20.0
10.0
0.0
-15
-10
-5
0
5
10
15
R/P ACTH ratio


L/P PRL ratio
12.0
10.0
8.0
6.0
4.0
2.0
0.0
-15
-10
-5
0
5
10
15
L/P PRL ratio


R/P PRL ratio
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-15
-10
-5
0
5
10
15
R/P PRL ratio

Evaluation of Pituitary Cushing's with IPSS

- Test performance characteristics:
  - Sensitivity 88-100%, Specificity 67 to 100% depending on study (Zampetti et al. Endocr Connect. 2016 Jul; 5(4): R12–R25.)
- **False positive:**
  - Must have **hypercortisolism** - ***if ectopic ACTH is treated (e.g. with ketoconazole to normalize Cortisol levels, bilateral adrenalecctomy pituitary corticotrophs will be susceptible to stimulation)***
  - Tumor in cavernous sinus (rare)
  - Ectopic CRH producing tumor
  - Intermittent release of Ectopic ACTH/Cortisol (cyclic disease)
- False negative up to 11% due to anomalous venous drainage or incorrect catheter placement – sampling prolactin level may help to correct for this

Practical tips for IPSS

- Confirm CRH availability – only available vial was expired
  - Acthrel (corticorelin ovine triflutate)
- Must be prepared by pharmacy and used within 30 minutes, so confirm that someone will be able to do this and tube to the appropriate location (phone number and tube station numbers)
- Verify with the clinical lab that someone is available to process the samples, review your plan. ***There are lab order templates available but these may need to be updated***
- Ice buckets, pre-labeled EDTA-tubes, lab order sheets x3, plastic biohazard bags for each set of tubes
- 4-5 people to assist
  - R IPSS
  - L IPSS
  - Peripheral
  - Time keeper
  - Extra person/runner
- Hand-deliver the samples to the lab!

Patient update

- S/p transsphenoidal hypophysectomy on 12/15/17
  - Course complicated by transient DI
  - On hydrocortisone replacement
- Op report:
  - The tumor was noted to extrude right away. It was clearly different consistency than the surrounding pituitary gland. The tumor was very liquid and soft... The tumor was then removed in its entirety…Great extensive inspection of the entire area under the endoscope was performed… and no further tumor could be seen.
- Final path:
  - Histologic sections show a few nests of normal pituitary parenchyma and a proliferation of rather monomorphic bland cells that stain for synaptophysin and ACTH. The MIB-1 proliferative index is low.
  - The cells are negative for TSH, prolactin, FSH, LH, and GH. Overall the features are support the diagnosis of an ACTH secreting adenoma.
- Follow up in Endocrine clinic next week

Thank you!