THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

AT THE FOREFRONT OF MEDICINE®

30 y.o female with low cortisol

Endorama

Thaer Idrees M.D.

First year adult endocrine fellow

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

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I have no relevant financial relationships with any commercial interests

OBJECTIVES

- Symptoms, signs and laboratory findings of primary and secondary adrenal insufficiency
- Common etiologies for secondary adrenal insufficiency
- Less common etiologies for secondary adrenal insufficiency

HPI

30 yo F with PMH of STEMI (12/2017, balloon angioplasty to OM1 at NWH), R ulnar artery thrombosis, questionable hx of CVAs

CC: Diffuse bruising and abdominal pain

Consult: Low cortisol and low BP

- Generalized spontanouse bruising started 10 days PTA, predominantly on the legs. No trauma or falls, but on Plavix and stopped ASA recently
- Extreme epigastric pain started the day before along with severe headache and dizziness
- + photophobia, phonophobia, and nausea

PMH:

- STEMI 12/2017 NWM. OM1 s/p balloon angioplasty (unable to be stented)?dissection
- R ulnar arterial clot (after RUE swelling)
- Anxiety
- Strokes

PSH: None

PFH:

- Diabetes Maternal Grandfather
- High Cholesterol Maternal Grandfather
- Diabetes Paternal Grandfather
- High Cholesterol Paternal Grandfather
- High Cholesterol Father
- Hypertension Mother
- Heart Disease Maternal Grandfather
- Hypertension Maternal Grandfather
- Heart Disease Paternal Grandfather
- Hypertension Paternal Grandfather
- Hypertension Father
- Thyroid Disorder Maternal Grandmother

SH: Patient was born in India and raised in England. She completed graduate school in psychology

PTA Meds:

Sertraline Clonazepam Atorvastatin
Buspar Wellbutrin Ambien PRN Amlodipine

Allergies:

Colchicine, Norco

REVIEW OF SYSTEMS

- Constitutional: **Positive for malaise/fatigue and weight loss**. Negative for diaphoresis and fever
- HENT: Negative for ear discharge, hearing loss and tinnitus
- Eyes: Negative for blurred vision and double vision
- Respiratory: Negative for cough, sputum production and shortness of breath
- Cardiovascular: Negative for palpitations and claudication
- Gastrointestinal: **Positive for abdominal pain**, **nausea and vomiting.** Negative for diarrhea
- Genitourinary: Negative for dysuria
- Musculoskeletal**: Positive for back pain and myalgias**. Negative for falls
- Skin: Negative for rash
- Neurological: Negative for dizziness, tingling, tremors, speech change and headaches
- Endo/Heme/Allergies: Negative for environmental allergies
- Psychiatric/Behavioral: Negative for depression. The **patient is nervous/anxious**

All other systems reviewed and are negative

PHYSICAL EXAM

- BP **90/53** | Pulse 80 | Temp (98.4 °F) | Resp 16 | Ht (5' 3") | Wt (128 lb) | SpO2 96% | BMI 22.68 kg/m2

- Constitutional: **in moderate** distress
- HEENT: EOMI, oropharynx clear
- Neck: supple, no thyromegaly, no acanthosis nigricans
- Cardiovascular: regular rate, no extra heart sounds
- Pulmonary/Chest: good respiratory effort, clear to auscultation bilaterally
- Abdomen: bowel sounds present, soft, **tender**, no violaceous straie, **bruises**
- Musculoskeletal: moving all extremities, **bruises different ages.**
- Neurological: sensation intact to light touch, strength 4/5 symmetrical
- Skin: warm, dry
- Psychiatric: not agitated, **anxious**

LABS

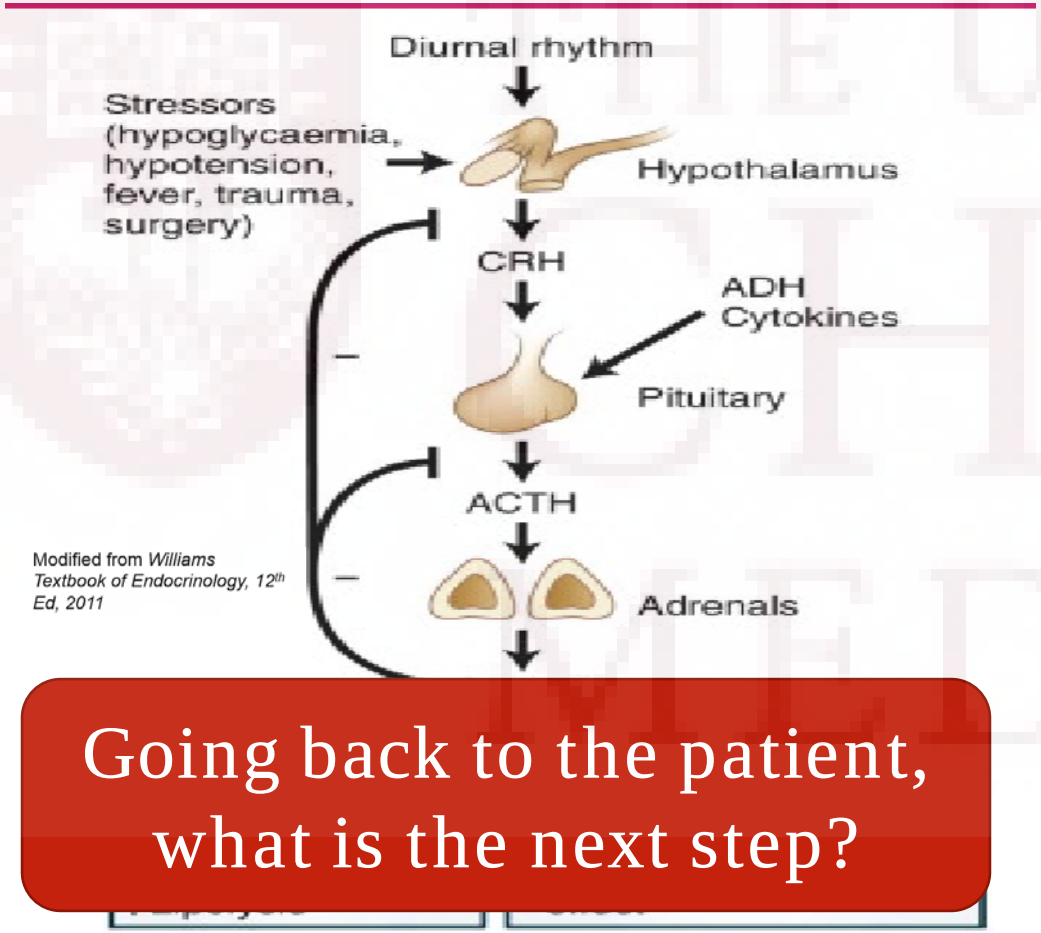
Adrenal crisis?

WBC	5.3
RBC	4.06
Hemoglobin	12.2
Hematocrit	36.8
MCV	90.6
MCH	30.0
MCHC	33.2
RBC Dist Width	13.5
Platelet Count	275
Mean Platelet Volume	13.0 ▲

- CK 201
- Lipase 86
- **Cortisol 0.7 (6 AM)**
- Cortisol at NWMH 3 months PTA: **17**

BASIC & COMPREHENSIVE	
Glucose, Ser/Plasma	110 * ▲
Sodium	143
Potassium, Ser/Plasma	3.5
Chloride	112 ▲
Carbon Dioxide	23
Anion Gap	8
BUN	10
Creatinine	0.6
GFR Estimate (Calc)	117 *
Calcium	8.1 ▼
Inorganic Phosphate	3.9
Magnesium	2.0
Total Protein	5.4 * ▼
Albumin	3.2 * ▼
Bilirubin, Total	0.1
Bilirubin, Conjugated	<0.1
Bilirubin, Unconju...	0.1
Alk Phos, Serum	69
AST (SGOT)	22
ALT (SGPT)	20

ACUTE ADRENAL INSUFFICIENCY



Going back to the patient, what is the next step?

Characteristics	Primary	Secondary
N, V, and abdominal pain	Prominent	Less common
Shock and low BP	XX	X
Hyperpigmentation (if acute on chronic)	XX	--
Fatigue and weakness	XX	XX
Low BG	XX	XX
Low Na	XX	X
High K	XX	--

Schrier et al., J Am Soc Nephrol. 2006

LABS

	Ref. Range and Units	1 9/29/2018 0700	2 9/29/2018 0630	3 9/29/2018 0622	4 9/28/2018 1123	5 9/28/2018 0602
Cortisol	Latest Units: ug/dL	*10.1 **	*6.9 **	*0.7 **		*0.7 **
ACTH	Latest Range: <52 pg/mL			*10.1*	*1.1*	

Differential Diagnosis?

Other labs?

Does report menstrual abnormalities for last 3 months

	Ref. Range and Units	10/2/2018 0747	9/29/2018 0630	9/28/2018 0602
THYROID FUNCTION				
Thyroxine, Free	Latest Range: 0.9 - 1.7 ng/dL	*0.74 **		*0.81 **
Triiodothyronine, ...	Latest Range: 80 - 195 ng/dL		*81*	
Thyroxine, Total	Latest Range: 5.0 - 11.6 ug/dL		*4.1*	
Thyrotropin	Latest Range: 0.30 - 4.00 mcU/mL	*2.06*		*0.90*

	Ref. Range and Units	10/2/2018 0747
Estradiol, Serum	Latest Units: pg/mL	*46 **
Luteinizing Hormone	Latest Units: u[iU]/mL	*13.3 **
FSH	Latest Units: u[iU]/mL	*6.6 **

Prolactin	Latest Range: 4.8 - 23.3 ng/mL	*19.72*

HOSPITAL COURSE

Headache

- Admitted few months ago with acute on chronic headache after a stroke. Reported only Dilaudid and morphine work
- Multiple admissions in the past at different institutions with headache that required Diluadid
- Neurology: Topamax (patient did not use)

Bruising

- Hematology: negative work up including PT/PTT, fibrinogen, Factor VIII, paraneoplastic panel, vWD panel, D-dimer
- Hypercoagulable work up has been negative for anticardiolipin, vWF assay, anti-beta2-glycoprotein antibodies, lupus anticoagulant testing, normal PTG20210A and factor V, Protein C and S
- The only positive work up was high ANA (vascular purpura?) ➔ consult Rheumatology to r/o vasculitis

HOSPITAL COURSE

Rheumatology

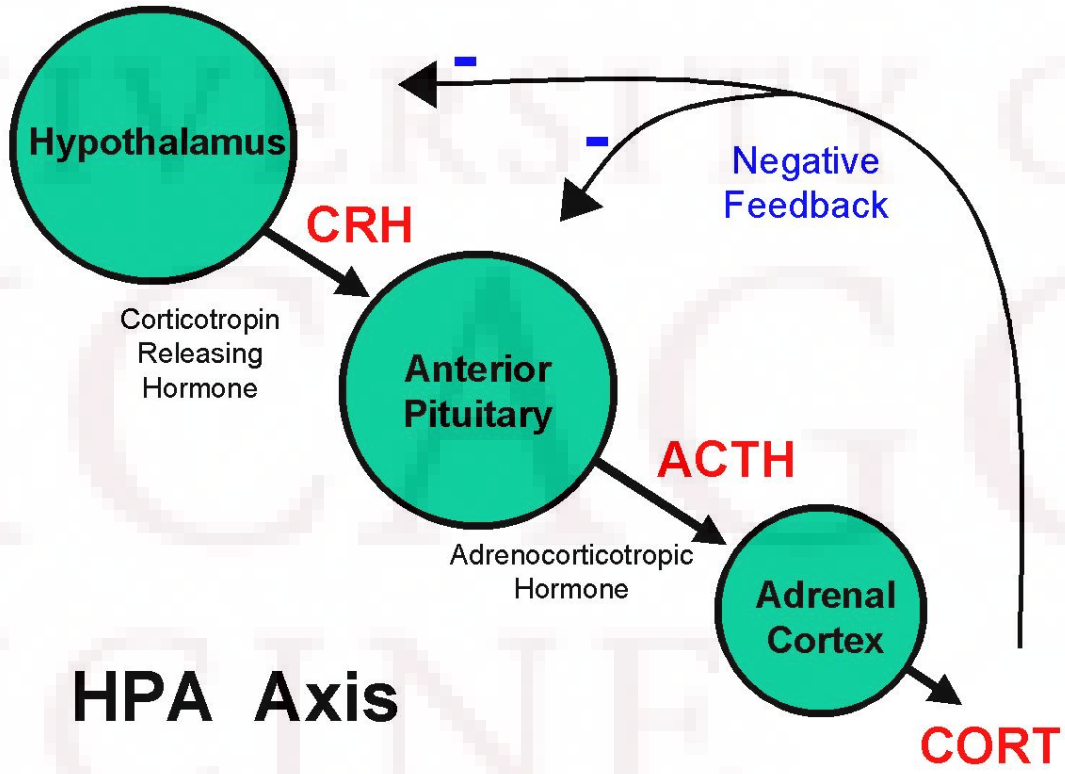
- She had positive **ANA 1:1280,** but negative for dsDNA, anti-histone, Jo1, RF, ANCA, anticardiolipin IgG and IgM, B2GP IgG IgA IgM
- Less likely systemic vasculitis, no end-organ damage, no fever/ weight loss/ elevation of inflammatory markers to suggest an ongoing inflammatory process

Psych

- Significant domestic violence

SECONDARY ADRENAL INSUFFICIENCY

Hypothalamic diseases
Mass lesions – Benign (craniopharyngiomas) and malignant tumors (metastatic from lung, breast, etc)
Radiation – For CNS and nasopharyngeal malignancies
Infiltrative lesions – Sarcoidosis, Langerhans cell histiocytosis
Infections – Tuberculous meningitis
Other – Traumatic brain injury, stroke
Pituitary diseases
Mass lesions – Pituitary adenomas, other benign tumors, cysts
Pituitary surgery
Pituitary radiation
Infiltrative lesions – Hypophysitis, hemochromatosis
Infection/abscess
Infarction – Sheehan syndrome
Apoplexy
Genetic mutations
Empty sella

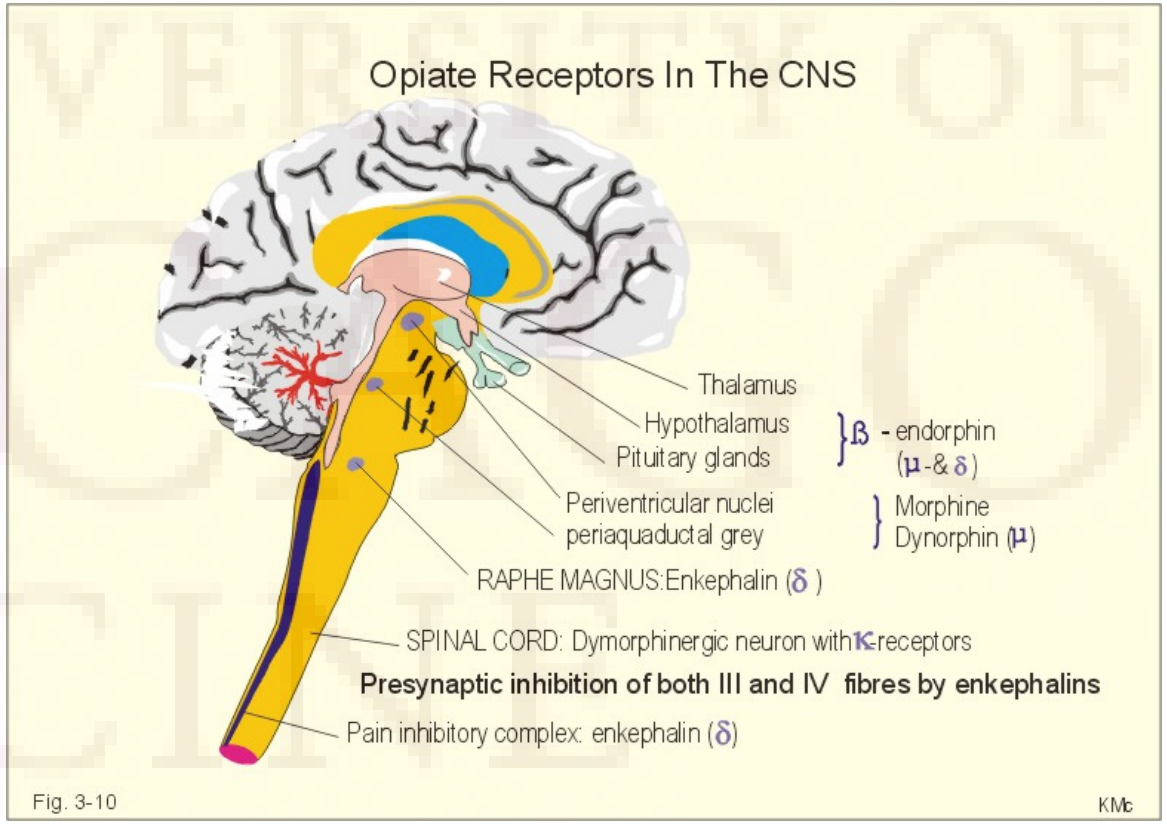


The most common causes of secondary adrenal insufficiency are:

- Abrupt cessation of high-dose glucocorticoid therapy
- Correction (cure) of hypercortisolism (Cushing's syndrome)

OPIOIDS & ADRENAL INSUFFICIENCY

- Opiates may suppress the hypothalamic-pituitary-adrenal axis
- Eleven human studies suggested that long-term administration of opioids (oral, intravenous, or intrathecal) leads to suppression of the HPA axis
- Naloxone, an opioid receptor antagonist with a higher affinity for the **μ** receptor, given in high doses (>10 mg) to healthy volunteers➔ increased cortisol levels and augmented corticotropin response to (CRH) stimulation



American College of Neuropsychopharmacology

Donegan et al., Mayo Clin Proc. 2018 .

Morphine	Allolio et al,[4] 1987	6 Males and 1 female (placebo-controlled)	Oral	Single dose	30-mg slow release	Reduction in cortisol (124 vs 275 nmol/L), corticotropin (1.2 vs 2.9 pmol/L), and β-endorphin (28 vs 47 pmol/L) with decreased peak response to CRH
	Palm et al,[11] 1997	5 (Double-blind, randomized, placebo-controlled, crossover)	Oral	1 wk	Day 1, 60 mg; day 2, 120 mg; day 3-7, 180 mg	Significant reduction in cortisol and corticotropin (24 vs 10 pg/mL) with reduced response in CRH stimulation (in 2 patients tested)
	Abs et al,[12] 2000	73 Received opioids and 20 chronic non-cancer pain—matched controls	Intrathecal	Long-term (mean, 26.6±16.3 mo)	Mean daily 4.8±3.2 mg (morphine, n=68; hydromor-phone, n=5)	Decreased urinary free cortisol (36 vs 50.7 μg/L) and a reduced peak cortisol after ITT (245.4 vs 300.8 μg/L)
Fentanyl	Oltmanns et al,[13] 2005	1 (Case report)	Patch	2 y	480 mg	Adrenal crisis with reduced response to CRH
	Schimke et al,[14] 2009	1 (Case report)	Patch	7 mo	180 mg	Secondary adrenal insufficiency with failure of cortisol to increase following corticotropin stimulation
Tramadol	Debono et al,[15] 2011	1 (Case report)	Oral	3 y	15 mg	Low basal cortisol (54

Opioid	Reference, year	No. of participants	MOA	Duration	Dose (MEDD)[b]	Effect on HPA
Mixed opioids	Gibb et al,[17] 2016	48 Patients with chronic noncancer pain (25 female and 23 male)	Oral: tramadol, oxycodone, morphine, or dihydroco-deine Patch: fentanyl or buprenor-phine	Long-term (at least 6 mo use)	Median, 68 mg (40-153 mg)	4 (8.3%) patients had a basal cortisol level of <100 nmol/L, 3 of whom had inadequate response to corticotropin stimulation test
	Merdin et al,[18] 2016	20 Patients with chronic cancer-associated pain	Not specified	Long-term (≥1 mo use)	Median, 180 mg/d (10-420 mg/d)	Serum cortisol level was lower than the normal reference range in 3 patients (15%) and higher than normal range in 8 (40%) (reference range, 4.3-22.4 μg/dL). Corticotropin level was normal in 17 of 18 patients (94.5%) (reference range, 0-65 pg/mL)
	Rhodin et al,[19] 2010	39 Patients with chronic noncancer pain, 20 chronic non-cancer controls	Methadone and slow-release morphine or oxycodone	Long-term (>1 y)	Mean in males treated with methadone, 1596 mg; and in females. 1322 mg	Peak corticotropin level following CRH was higher in the opioid-treated group than in controls (73.7 IE/L vs 39.2 IE/l) with no difference in basal or peak cortisol level

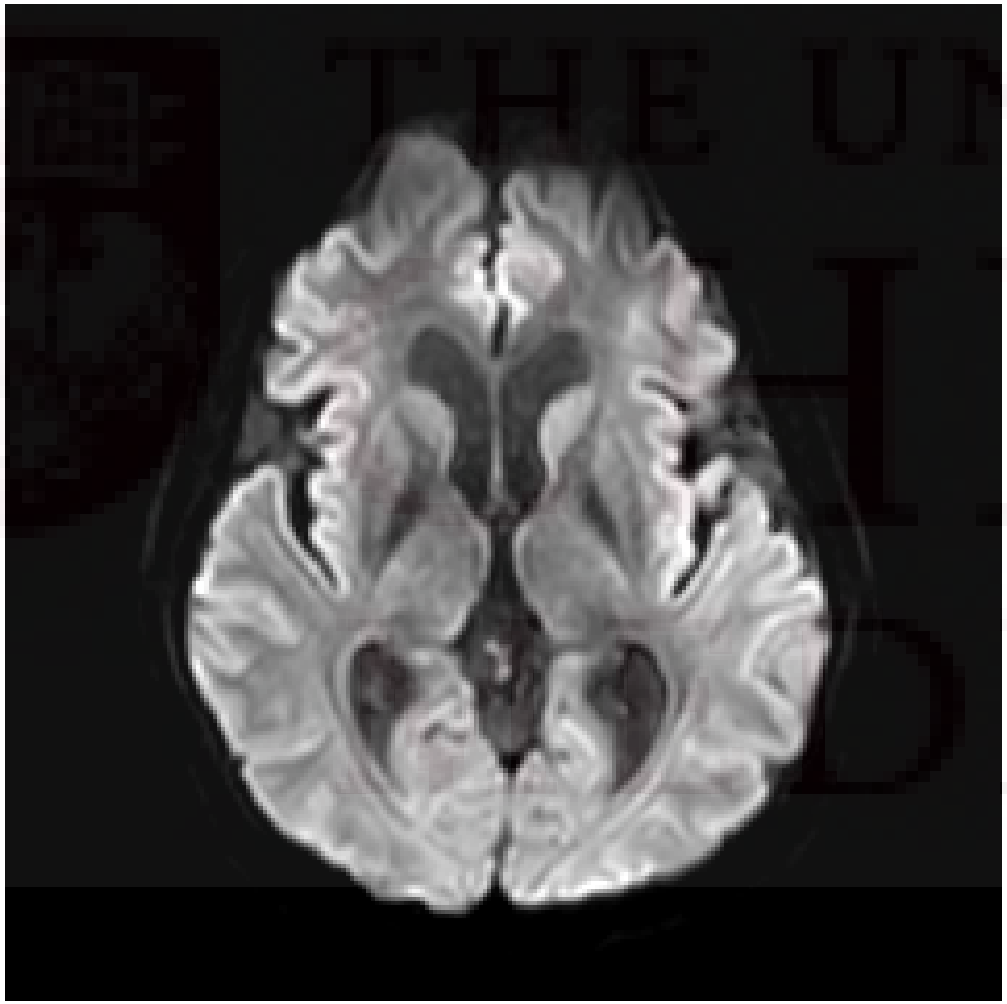
CONCLUSION

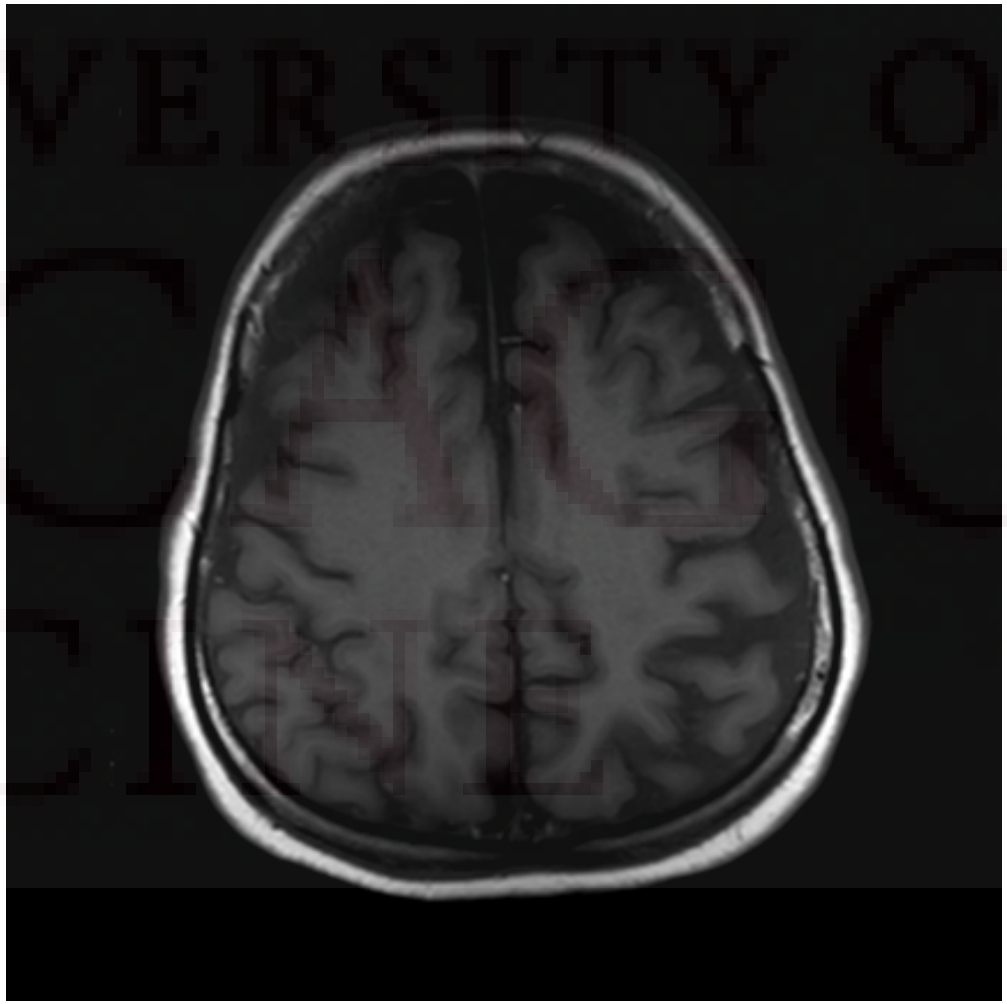
- Available data from small heterogeneous studies suggest that 9% to 29% of patients receiving long-term treatment with opiates have development of adrenal insufficiency
- Careful consideration of OIAI in any patient receiving long term opiate therapy who manifests symptoms and signs suggestive of adrenal insufficiency

BACK TO THE PATIENT

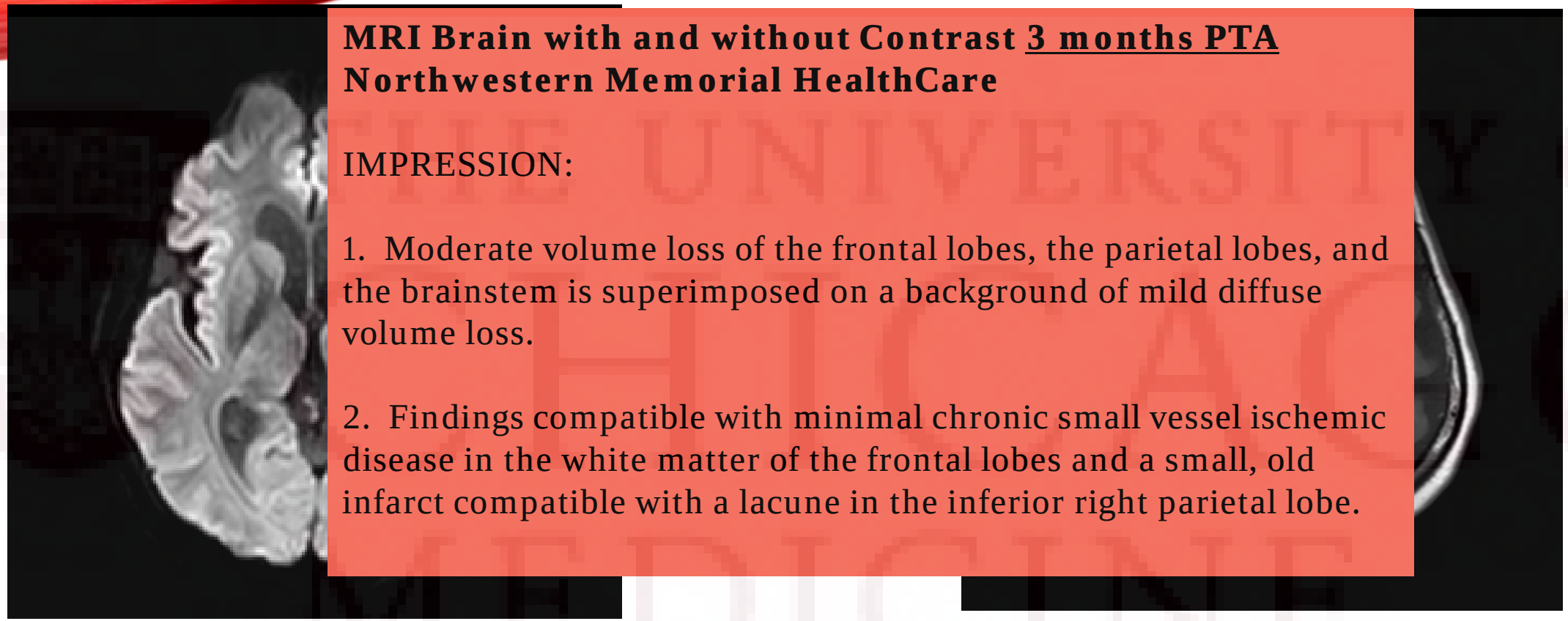
Imaging loading…….

MRI BRIAN WO





MRI BRIAN WO



MRI Brain with and without Contrast <u>3 months PTA</u>
Northwestern Memorial HealthCare

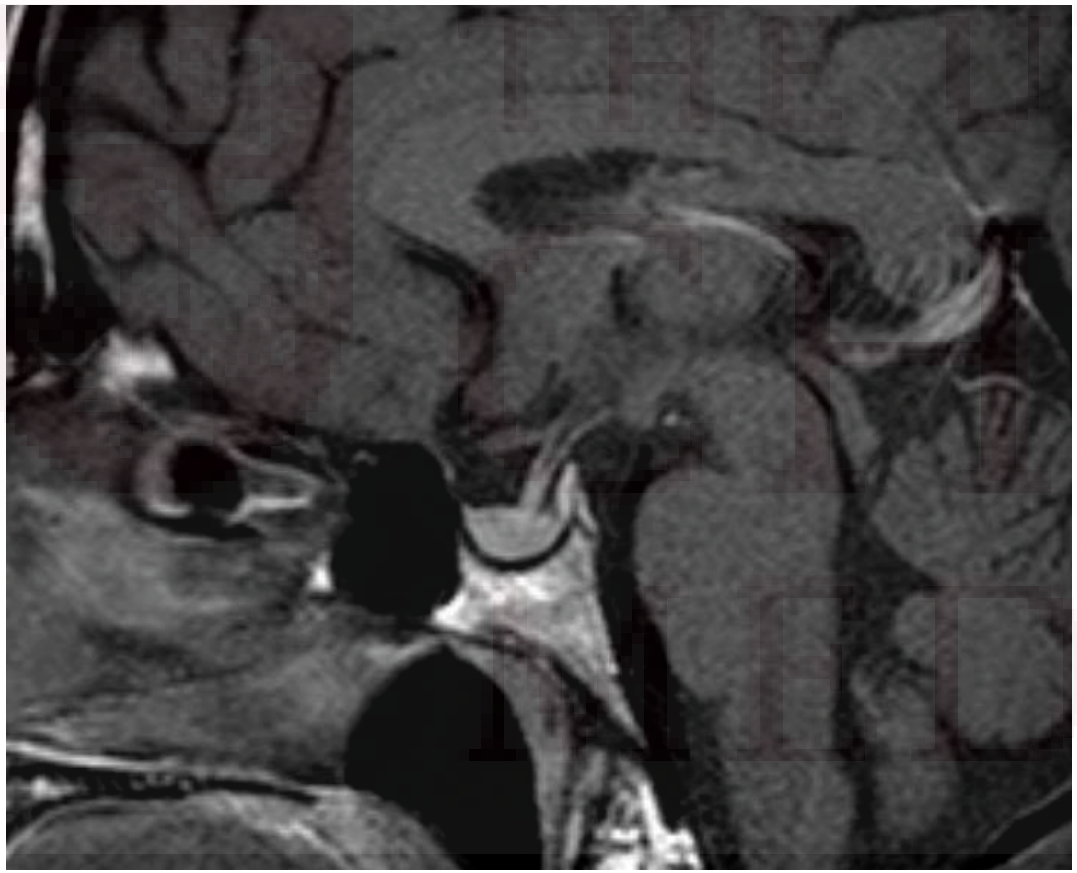
IMPRESSION:

1. Moderate volume loss of the frontal lobes, the parietal lobes, and the brainstem is superimposed on a background of mild diffuse volume loss.

2. Findings compatible with minimal chronic small vessel ischemic disease in the white matter of the frontal lobes and a small, old infarct compatible with a lacune in the inferior right parietal lobe.

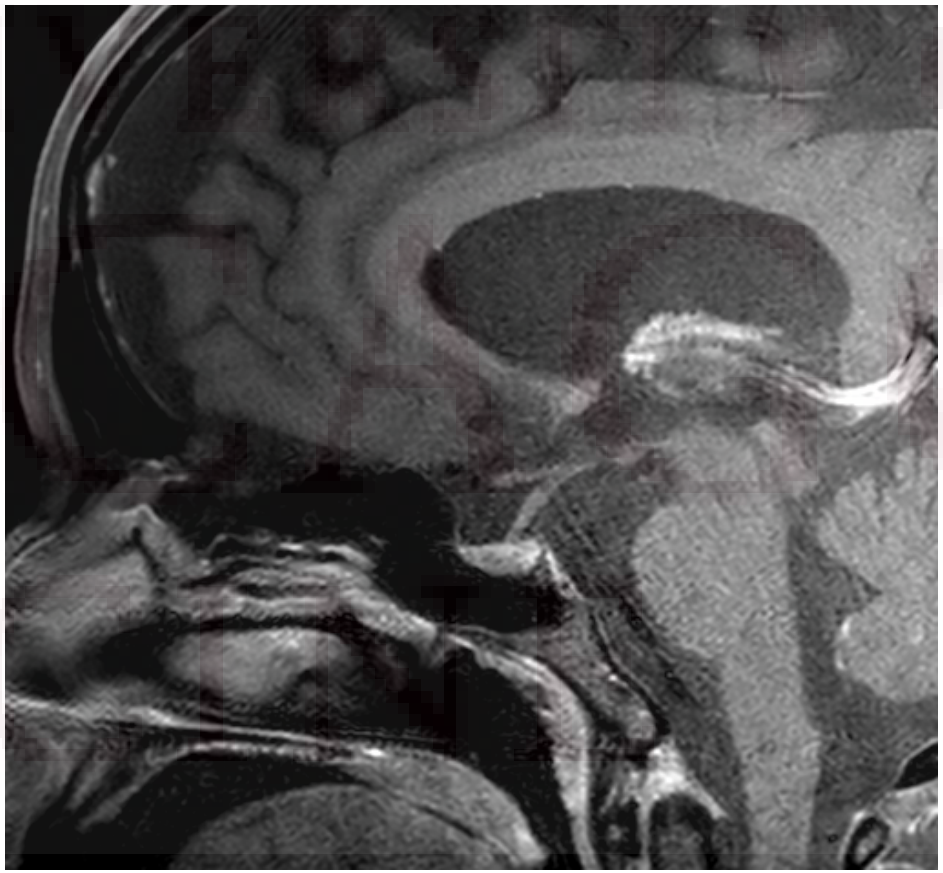
IMPRESSION:
1. Disproportionate volume loss in the bilateral frontal lobes may indicate a neurodegenerative or developmental condition
2. Nonspecific small lesions (lacunar infarcts) in the bilateral frontal lobe white matter
3. No evidence of acute intracranial hemorrhage, mass, or acute infarct

MRI PITUITARY



Normal MRI from literature

The patient

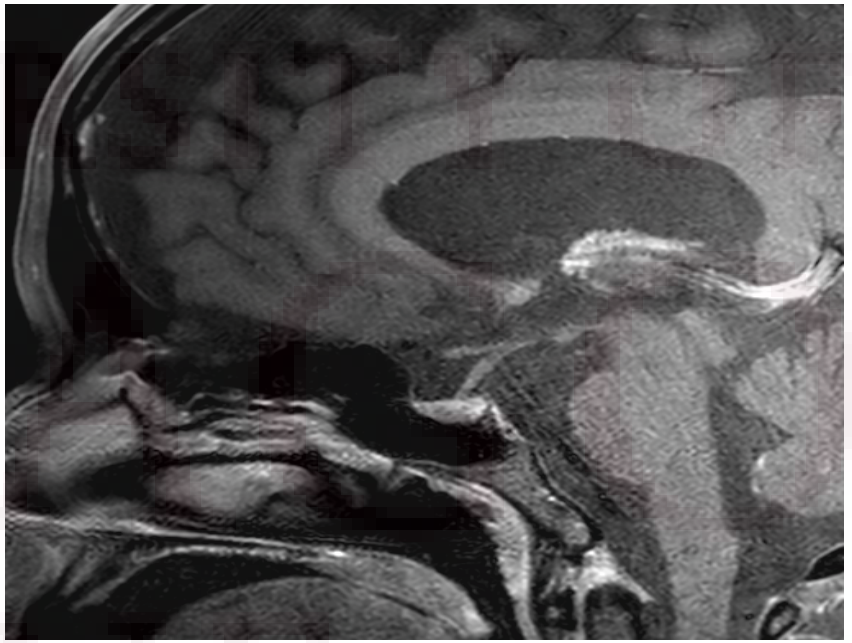


IMPRESSION: no discernible pituitary lesions

De Groot LJ, Chrousos G, Dungan K, et al., editors. South Dartmouth (MA):

NEUROSURGERY

- *The patient's pituitary gland is small asymmetric and heterogenous, which consists with **pituitary atrophy***
- *This is likely secondary to a remote pituitary infarct or resolved hypophysitis*
- *Given her cardiovascular risk factors, remote pituitary infarct is more likely*
- *While this could explain hypopituitarism, there is no actionable structural lesion or other surgical pathology, no evidence of tumor*



PITUITARY INFARCTION (PITUITARY APOPLEXY)

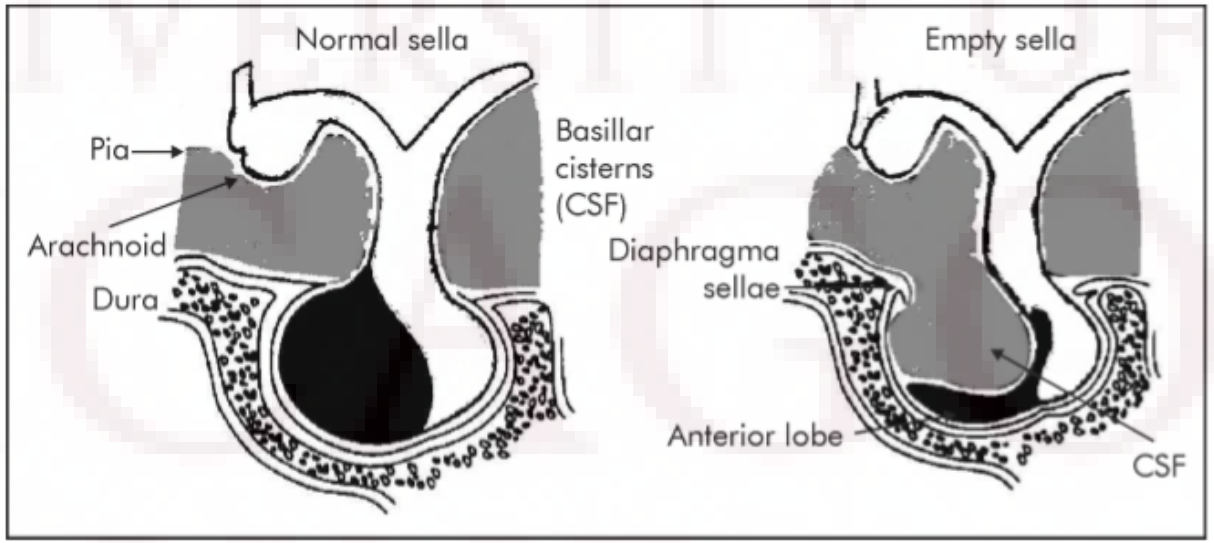
- Pituitary adenomas are particularly prone to hemorrhage and necrosis
- Risk factors such as hypertension, medications, major surgeries, coagulopathies either primary or following medications or infection, head injury, radiation
- Vascular changes after pituitary irradiation often result in chronic hypoperfusion of the pituitary gland
- Even sometimes with coughing, or sneezing! (bleeding into an adenoma)

Biousse et al., *Journal of Neurology 2001*

PITUITARY ATROPHY

Empty Sella syndrome

- Increased pressure in the suprasellar subarachnoid space or by reduction in the size of the pituitary gland
- Shrinkage of the pituitary gland may occur after post-partum pituitary necrosis (Sheehan's syndrome) or pituitary infarction in patients with vascular diseases, diabetes, increased intracranial pressure, head injury, meningitis, or cavernous sinus thrombosi



Empty Sella Syndrome JK Agarwal, RK Sahay, SK Bhadada, Vijay Sekhar Reddy, NK

HYPOPHYSITIS

- AI: inflammatory infiltrate of the pituitary gland
- Symptoms of sellar compression, represented by headache and visual disturbances, are the most common and usually the initial complaint
- Symptoms are due to a partial or complete deficit of the anterior pituitary hormones, mainly ACTH followed by TSH, gonadotropins
- In contrast to other forms of hypopituitarism, ACTH deficiency is most common in patients with lymphocytic hypophysitis
- Over time the pituitary gland may atrophy, leaving an empty sella

- Primary forms
  - Lymphocytic (autoimmune)
  - Granulomatous
  - Xanthomatous
- Secondary forms
  - Local lesions
    - Germinomas
    - Rathke's cleft cysts
    - Craniopharyngiomas
    - Pituitary adenomas
  - Systemic diseases
    - Sarcoidosis
    - Wegner's granulomatosis
    - Langerhans cell hisitocytosis
    - Syphilis
    - Tuberculosis

Patrizio et al., Endo rev 2005

immunotherapy

Pituitary Apoplexy

Claire Briet, Sylvie Salenave, Jean-François Bonneville, Edward R. Laws, and Philippe Chanson

All these patients had adenoma

Angiography	Reichenthal, 1980	57	40	M	NA	Carotid angiography
	Suga, 1996	59	29	F	PRL	Cerebral angiography
	Louwerens, 1996	56	32	M	GH	Cerebral angiography
	Skljarevski, 2003	58	66	M	NF	Coronarography

Closed head trauma	Holness, 1983	95	39	M	NF	Minor head trauma motor vehicle
	Tamasawa, 1988	99	34	M	GH	Fall from the back of a truck
	Itoyama,1990	97	45	M	NA	Fall 2 meters
	Uchiyama, 1999	100	66	M	NA	Fall 15 meters
	Uchiyama, 1999	100	60	F	NA	Mild (fall from his height)
	Horie, 2002	96	56	F	NA	Traffic car accident
	Smidt, 2007	98	30	M	NA	Minor head trauma
	Dev, 2007	94	40	M	necrosis	Mild cranial trauma (road traffic)
	Bao, 2007	93	79	M	Not operated	Mild cranial trauma (fall)

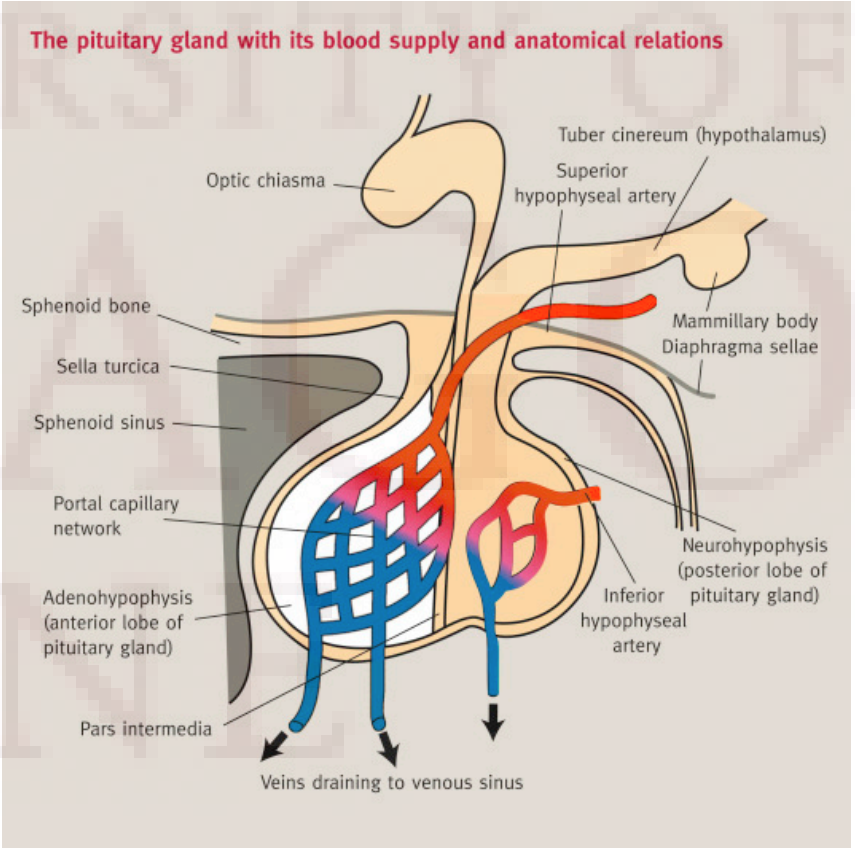
Briet et al., endocrine Reviews, Volume 36, Issue 6, 1 December

BRAIN INJURY AND HYPOPITUITARY

- Anterior-pituitary dysfunction is more common than posterior-pituitary dysfunction in survivors of TBI
- In a meta-analysis, Schneider et al included 1,015 TBI patients from ten cross-sectional and four prospective studies the pooled prevalence of anterior hypopituitarism has been reported as 27.5% (95% confidence interval 22.8–28.9)

Pathophysiology

- Long superior hypophyseal arteries provide the anterior pituitary gland with 70–90% of its blood supply (vulnerable to mechanical trauma, intracranial hypertension, low cerebral blood flow and brain swelling)
- Pituitary glands confinement within the bony sella



Hillary et al., Sur. (Oxford)2017

Javed, Zeeshan et al. Indian journal of endocrinology and metabolism (2015)

BIOTIN AND CORTISOL

- https://www.healthcare.uiowa.edu/path_handbook/Appendix/Chem/BiotinImmunoassayTables.pdf

BACK TO OUR PATIENT

Treatment plan

- Hydrocortisone 40 mg in AM and 20 mg in PM
- Decreased next day to 20 mg in AM and 10 mg in PM (blood pressure slightly improved)
- Started on Synthroid 25 mcg daily
- Was discharged on maintenance dose of hydrocortisone (20,10) and Synthroid
- Lost to follow up and missed endocrine appointment

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THANK YOU

Questions/comments?