



56-year-old man with concern  
for adrenal insufficiency

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Endorama

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# History of Present Illness

- 56-year-old man with history of cirrhosis secondary to steatohepatitis, hepatitis C, and ETOH use, complicated by refractory ascites requiring weekly paracenteses. A prior cell count had revealed WBC of 1930 with lymphocytic predominance (74%). He was admitted for peritoneal biopsy to assess for lymphocytic ascites and possible TIPS procedure.
- Endocrine was consulted for concern of adrenal insufficiency.

# Past Medical History

- Cirrhosis
- Diabetes mellitus, type 2
  - Diagnosed 20 years ago
  - Currently on Lantus 54 units in AM and 38 units in PM and glipizide 10 mg BID.
  - Per patient, fasting BS range 80-110 and before meals 130-150. Rare lows.
  - In house, same Lantus regimen + NISS 1 units for 50 >130.
- Chronic obstructive pulmonary disease
- Congestive heart failure
- Hypertension
- Chronic kidney disease
- Barrett's esophagus
- Anxiety disorder

# Past Medical History cont.

## ■ Medications:

- Albumin infusions
- Amitriptyline 50 mg qhs
- Calcium 600 mg + vitamin D 200 IU BID
- Carvediol 6.25 mg BID
- Clonazepam 0.5 mg TID
- Esomeprazole 40 mg dialy
- Gemfibrozil 600 mg BID
- Multivitamin daily
- Glargine 54 units in AM and 38 units in PM
- Novolog ISS
- Oxycodone 10 mg q4 hr prn
- Pregabalin 100 mg BID
- Rifaximin 550 mg BID
- Zinc 220 mg BID

## ■ Allergies:

- Pencillin G

# Past Medical History cont.

## ■ Social History:

- Married with 2 grown children.
- Quit tobacco use in 11/2001, smoked 2ppd x 40 years
- Quit ETOH use in 1984.
- Last used IV drugs 20 years ago.

## ■ Family History:

- Maternal grandparents with diabetes.
- One sister died of emphysema, smoker.
- Another sister has emphysema, s/p lung transplant, smoker.
- Brother died of Wegener's disease.
- Daughter with prolactinoma.

## ■ ROS:

- Abdominal distension but no pain.
- No nausea, vomiting.
- No lightheadedness, dizziness.
- No voice changes, changes in facial hair.
- Poor libido.

# Physical Exam

- Ht 185.4 cm (6' 0.99"), Wt 106.9 kg (235 lb 10.8 oz), BMI 31.10 kg/m<sup>2</sup>
- 96.4 °F, BP 135/65 (100-130s/50s), Pulse 87, Resp 20, SpO<sub>2</sub> 96% on RA
- Constitutional: Patient appears chronically ill, in no acute distress.
- Eyes: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- ENT: Mucous membranes moist. No hyperpigmentation of the buccal mucosa.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm and rate. No murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft, nontender, distended.
- Musculoskeletal/extremities: No peripheral edema.
- Neurological: Alert and oriented to person, place, and date. Normal deep tendon reflexes.
- Skin: Skin is warm and dry. No hyperpigmented scars.
- Psychiatric: Normal mood and affect.

# [ Laboratory Data ]

$\frac{135 \quad 105 \quad 40}{4.2 \quad 20 \quad 1.7} \left\{ \begin{array}{l} 183 \\ 153 \end{array} \right.$

Ca 7.3, Phos 4.1, Mg 2.0

~~$\frac{11.2}{33.1}$~~   
4.5 153

59%N, 22%L, 13%M, 5%E, 1%B

Total protein 4, albumin 3.1, total bili 0.4, alk phos 23,  
AST 25, ALT 9

$\frac{128 \quad 101 \quad 50}{5.2 \quad 20 \quad 1.9} \left\{ \begin{array}{l} 212 \\ 153 \end{array} \right.$

Ca 7.7, Phos 4.8

# Laboratory Data

- 6AM cortisol: 2.9
  - The following blood tests showed normalization of electrolytes to Na 134, K 4.6.
- Cort stim:
  - No baseline cortisol obtained.
  - 45 minutes after receiving cosyntropin, cortisol level was 3.7.



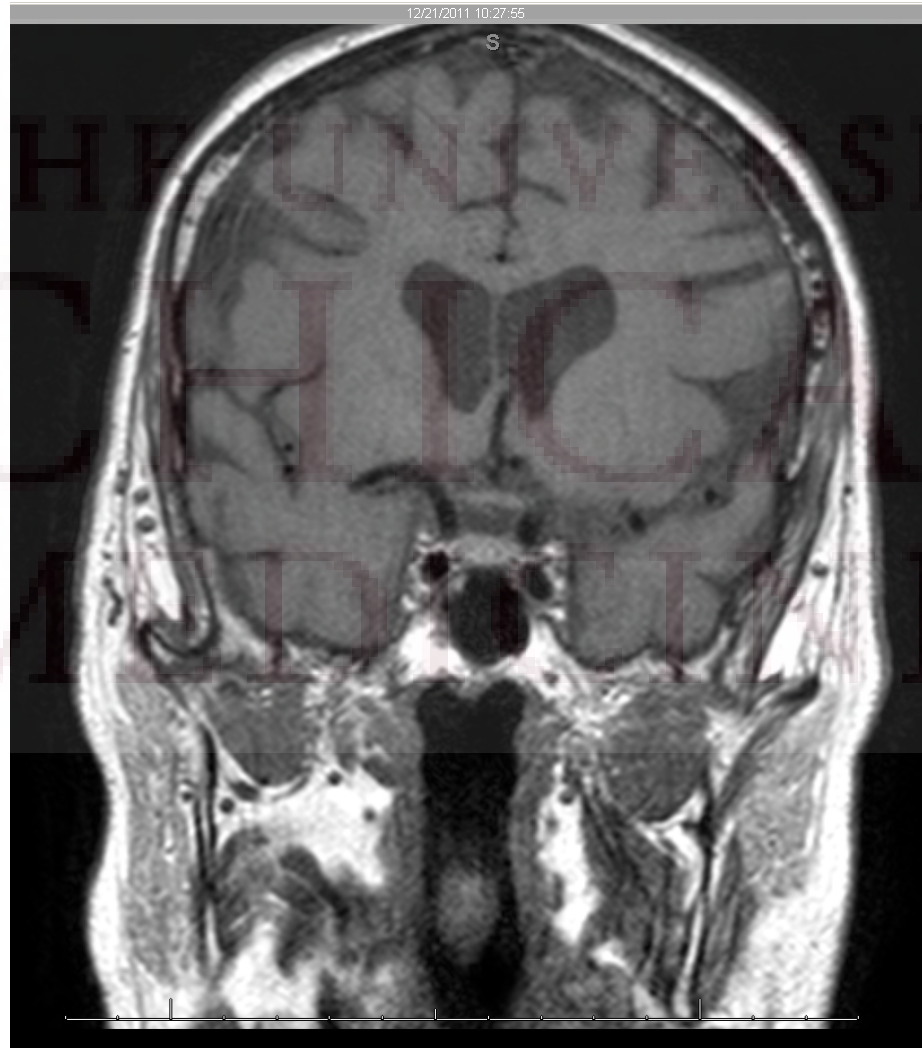
# Assessment & Plan:

- Adrenal function:
  - Low AM cortisol, did not appear to stim.
  - No signs or symptoms suggestive of adrenal insufficiency.
  - Recommended: repeat cort stim test at 6AM tomorrow with baseline cortisol and ACTH.
  - Hold off on replacement given no signs or symptoms.
- Diabetes mellitus type 2:
  - Please change Lantus to 30 units BID
  - Please add Novolog 15 units with meals.

# [ More labs ]

- 6:30 AM cort stim:
  - Cortisol 1.6 (ACTH <5.0) → 14.6 → 18.2
- Concern for secondary adrenal insufficiency.
  - Check PRL, TFTs.
  - Obtain MRI.
- Prolactin: 9.36
- TFTs:
  - TSH: 5.38
  - fT4 (0.9-1.7): 0.75
  - T4 (5-11.6): 5.5
  - T3 (80-195): 94
  - rT3 (160-353): 495

# [ MRI pituitary ]



# [ Assessment & Plan cont. ]

- Concern for secondary adrenal insufficiency
  - Start hydrocortisone 20 mg QAM and 5 mg QPM.
  - Outpatient insulin tolerance test.



# [ My Questions: ]

- Given hypoproteinemia in these patients, what other measures have been studied?
- What is a normal ACTH level?
- How reliable is the cort stim test in secondary adrenal insufficiency?
- How common is adrenal insufficiency in liver disease?

# Use of Other Measures

- Serum free cortisol:
  - >90% of cortisol is protein-bound
    - CBG, 70%:
      - Low capacity, high affinity
      - Becomes saturated at 25 mcg/dL of cortisol
      - In critically ill patients, decreased CBG concentration and binding affinity.
    - Albumin, 20%:
      - High capacity, low affinity
- Salivary cortisol:
  - Correlate free serum cortisol

# Serum Free Cortisol

- Prospective study of 43 clinically stable cirrhotic patients.
- All patients had cort stim with measurements of serum total and free cortisol levels.
- 58% had AI according to total cortisol levels.
- 12% had AI according to free cortisol levels.
  - All had AI by total cortisol levels.
- AI by total cortisol levels was not associated with worse outcomes, but there was a statistically significant increase in mortality with AI by free cortisol levels.

Table 4. Subgroup analysis of AI and non-AI patients according to the plasma free cortisol (PFC) criteria. A *p*-value of <0.05 is considered statistically significant.

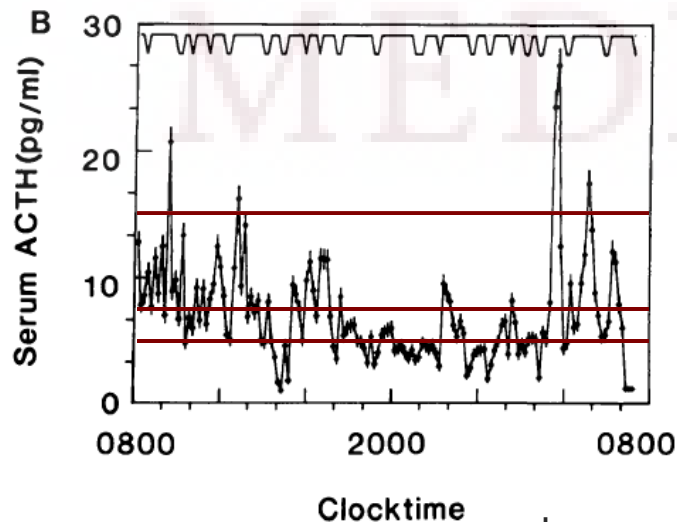
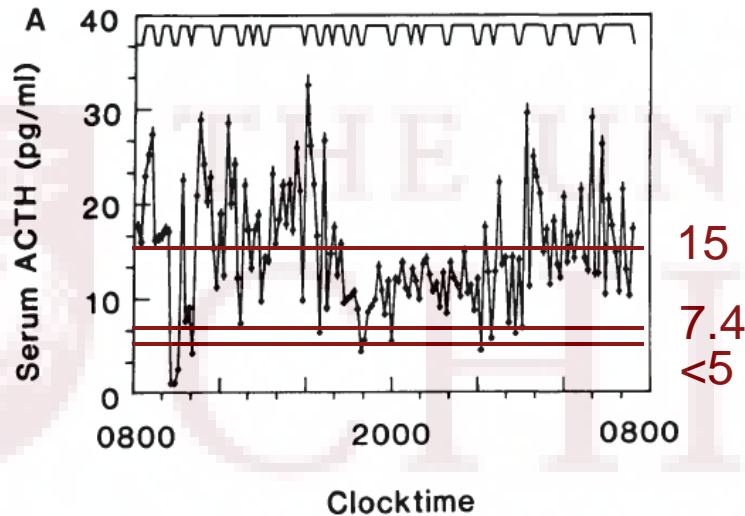
Mean (±SEM)	PFC-AI (n = 5)	PFC-Non AI (n = 38)	<i>p</i> value
Age	51 ± 1.6	52 ± 1.5	NS
Median Child Pugh	11 ± 0.7	9 ± 0.4	NS
Median MELD	19 ± 3.2	13 ± 0.8	0.03
CBG (mg/L)	11 ± 4.9	39 ± 2.3	NS
Albumin (g/L)	25 ± 4.1	29 ± 1.1	NS
Serum Na (μmol/L)	134 ± 2	136 ± 0.4	NS
Adverse Events (n)	4	9	NS
Death, n (%)	3 (60%)	2 (5%)	0.0007



# [ Salivary Cortisol ]

- Prospective study of 88 patients hospitalized for cirrhosis complications without shock.
- All patients had cort stim with measurements of serum total cortisol and salivary cortisol levels.
- 29 patients (33%) had AI according to serum total cortisol.
- 8 patients (9.1%) had AI according to salivary cortisol.
  - 7 patients had AI according to serum total cortisol.
- Hypoalbuminemia was the only factor associated with a discrepancy.
- Risk factors for AI by salivary cortisol levels were ascites and low HDL levels.

# Pulsatility of ACTH



- Profiles of ACTH levels in 2 normal men.
- Blood sampled at 10 min intervals.

# ACTH levels in Adrenal Insufficiency

- Controls, 55 subjects:
  - ACTH: 27 pg/mL (4-81)
  - Cortisol: 15 mcg/dL (8-33)
- Primary AI, 43 patients:
  - ACTH: 693 pg/mL (104-1,771)
  - Cortisol: 2.4 mcg/dL (0.4-7)
- Secondary AI, 46 patients:
  - ACTH: 14 pg/mL (8-75)
  - Cortisol: 7.3 mcg/dL (0.9-25)

# Cort Stim in Secondary Adrenal Insufficiency

	MET		HDT	LDT	VLDT
	ACTH (pmol/l)	11-DOC (nmol/l)	Cortisol (nmol/l)	Cortisol (nmol/l)	Cortisol (nmol/l)
Cut-off point	17.3	144.3	582.1 <b>(21)</b>	477.3 <b>(17)</b>	364.2 <b>(13)</b>
Sensitivity (%; 95% CI)	71.4 (41.9–91.4)	64.3 (35.2–87.1)	71.4 (41.9–91.4)	73.3 (44.9–92.0)	57.1 (28.9–82.2)
Specificity (%; 95% CI)	100 (80.3–100)	82.4 (56.6–96.0)	82.4 (56.6–96.0)	80 (51.9–95.4)	88.2 (63.5–98.2)
Accuracy (%)	87.1	74.2	77.4	76.7	74.2
ROC AUC (95% CI)	0.82 (0.65–0.93)	0.68 (0.49–0.84)	0.76 (0.57–0.89)	0.74 (0.55–0.88)	0.75 (0.56–0.88)
PPV (%)	100	75	76.9	78.6	80
NPV (%)	81	73.7	77.8	75.0	71.4
Cut-off point for sensitivity at 95%	85.6	372.3	1034.6	590.4	584.9
Cut-off point for specificity at 95%	18	2.8	113.1	55.2	88.3

- Salivary cortisol levels in cort stim:
  - Peak of 1.18 ug/dL, sensitivity 72%, specificity 86%

Giordano et al. [Clin Endocrinol \(Oxf\)](#). 2008 Jun;68(6):935-41.  
 Deutschbein et al. [Eur J Endocrinol](#). 2009 Jan;160(1):9-16.

# The Hepato-adrenal Syndrome

- High but variable prevalence:
  - Critically ill patients with liver disease: 33-66%
  - Non-critically ill patients with cirrhosis: 9-64%
  - Liver transplant patients: 61-92%
- No current consensus defining AI in liver disease.
  - ACTH stim: standard v. low dose
  - Serum total v. free cortisol concentrations

# The Hepato-adrenal Syndrome: Therapy

Authors	Patients	Steroid Dose	Outcome
Harry 2003	20 pts with acute liver failure	HC 300 mg/day	Reduction in vasopressor doses but no survival benefit. Higher incidence of infection.
Marik 2005	140 pts with acute or chronic liver disease	HC 100 mg q8 hrs	Reduction in NE dose at 24 hours. Lower mortality rate (26% v 46%, p=0.002).
Fernandez 2006	17 pts with cirrhosis, septic shock, and RAI	HC 50 mg q6 hrs	Resolution of septic shock (96 v. 58%, p=0.001). Increased hospital survival (64% v. 32%, p=0.003).
Arabi 2010	39 pts with cirrhosis and septic shock	HC 50 mg q6 hrs	Reduction in vasopressor doses. No benefit in 28 day mortality. Increase in shock relapse and GI bleed.

# [ Take Home Points ]

- Adrenal insufficiency is a difficult diagnosis in patients with hypoproteinemia.
- Serum free cortisol and salivary cortisol levels have been studied but there's not as much data.
- Insulin tolerance test is regarded as the gold standard for secondary adrenal insufficiency.
- Consider adrenal insufficiency in liver disease.

# References

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