68 year-old male with Adrenal Insufficiency

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Endorama

8/23/2012

HPI

- 68 yo M with HIV x 14 years (undetectable viral load, CD4 of 215), cryptogenic cirrhosis s/p TIPS complicated by refractory ascites admitted to the hospital from the Hepatology clinic on 7/30 with worsening ascites, SOB, hyponatremia consulted for adrenal insufficiency on 8/4.
- Since admission, serum sodium has been in low 120s.
- Underwent paracentesis-2.5 L removed, albumin given
- Underwent ACTH stim test on 7/30 at 9 pm where his cortisol 17 mcg/dl→22 mcg/dl, ACTH 50 pg/ml.
- Team started HC 20/10 mg from 7/31-8/2
- Has not been on chronic steroids

HPI

- Was in usual state of health until 1.5 months ago- had increasing abdominal distension due to recurrent ascites despite TIPS revision on Jan 2012
- Last week, diuretics increased from 20 to 40 mg of lasix, and from 25 to 50 mg of spironolactone
- Reports decreased urine output, Na slowly declining from 134->127->123->122. Creatinine stable 0.8

HPI

- Night before consult, he felt dizzy in the bathroom
- Bp 60/40s-improved with gentle hydration
- Hypoglycemic to 50s on day of consult
- Denies hx of diabetes and did not receive any insulin
- Complains of diffuse abdominal pain
- +Nausea, actively vomiting
- +lightheadedness, +dizziness
- Has been NPO for the past 2 days for CT abdomen/pelvis

- IMPRESSION: New pelvic anterior abdominal wall subcutaneous fluid collection is likely due to recent paracentesis with leak. Otherwise exam is stable since MRI of 8/1/2012.
  Adrenal glands are described as normal.

Past Medical History

- HIV x 14 years (CD4 count 215, undetectable viral load)
- Cryptogenic Cirrhosis s/p TIPS with recurrent ascites- being evaluated for possible liver transplant
- Nodular lesion in right hepatic lobe seen on MRI on 7/2012 concerning for HCC
- Esophageal Varies s/p banding
- Septic left knee joint s/p arthroscopy and antibiotics
- Hx of inguinal hernia repair

Social Hx

- Former smoker: 0.5 packs/day x 8 years, quit in 1979
- Alcohol: social drinker, quit in 1979
- Denies drug use
- Retired computer software developer
- Currently works as an Episcopal pastor
- Live with his wife and 2 sons

Family Hx

Mother- type 2 diabetes (was not on insulin) died at age 76 of stroke

Father- died of stroke at age 89

Both sons- healthy

Medications

Home Meds

Emtricitabine-Tenofivir (Truvada) 200-300 mg daily
Liponavir-ritonavir (Kaletra) 200-50 mg-2 tabs twice daily
Rifaximin 550 mg twice daily
Spironolactone 50 mg po daily
Valacyclovir 1000 mg po daily
Zinc sulfate 220 mg twice daily
Zinc gluconate 50 mg po daily
Rabeprazole (Aciphex) 20 mg po daily
Lactulose 667 mg/ml 30 ml daily
Lasix 40 mg po daily
Ciprofloxacin 500 mg po q24h
Vitamin D3 3,000 units daily

Hospital Meds

Lactulose 20 g daily
Tenofivir 300 mg po daily
Raltegravir 400 mg po BID
Rifaxmin 550 mg po BID
Valcyclovir 100 mg daily
Zinc sulfate 220 mg BID
Spironolactone 25 mg po daily
Lasix 20 mg po daily

Allergies: NKDA

Review of Systems: Denies fevers/chills, +abdominal distension, some SOB, denies Mental status changes

Physical Exam

VS: Temp 97.5 °F, bp 90/65, HR 62-70 RR 18-22
O2sat- 96-98% on RA, Height 5' 9" Weight- 159 lbs

Gen: thin, jaundiced, actively vomiting

HEENT: NCAT, +scleral icterus

Neck: supple, no thyromegaly

Heart: +S1/s2, no murmurs

Lungs: decreased bs at bases

Abdomen: soft, distended, +ascites , tender to palpation diffusely, no rebound tenderness

Extremities: no c/c/e

Neuro: Alert and oriented x 3

LABS

121 | 93 | 24 /56
5.5 | 20 |1.3 \

14.5 \ 11.0 /32
/ 30 \

AST-146 (8-37 U/L)
ALT 115 (8-35 U/L)
Alk phos- 138 (50-150 U/L)
Tbili- 28.6 (0.1- 1.0 ng/dl)
Tprotein- 5.3 (96.0 - 8.3 g/dL)
Albumin- 2.1 (3.5 - 5.0 g/dL)
Ammonia- 133 (0-70 mcg/dl)

PT- 35.6 (11.8-14.5 s)
INR- 3.9 (0.9-1.1)

TSH- 1.0 (0.30 - 4.00 mcU/mL)

7/30/2012 at 9 p.m. ACTH stim test
Cortisol. 17 mcg/dl→22.8 mcg/dl at 30 min. →22.6 mcg/dl at 60 min.

Questions

- 1.) Could he still have adrenal insufficiency due to liver dysfunction and history of cirrhosis?

- 2.) Is he also at risk for developing adrenal insufficiency due to his HIV status?

Hepato-Adrenal Syndrome

- In patients with cirrhosis, adrenal insufficiency during critical illness is associated with increased mortality, leading to what is termed “hepato-adrenal syndrome.”

- Exact mechanism still unclear, but Marik et. al suggested that low levels of HDL cholesterol may be responsible for the observed defects in adrenal function in liver disease since studies suggest that HDL is the preferred lipoprotein source of steroidogenic substrate in the adrenal gland.

- AI is also frequent in stable and in decompensated cirrhosis without sepsis, such as variceal bleeding (30-48%) and ascites (26%-64%).

Liver failure and AI

- Liver failure can contribute to AI by increasing levels of endotoxin and impairing cholesterol synthesis
- Bacterial infections that occur in patients with cirrhosis might be related to altered synthesis of adrenal cortisol, and bacterial and viral products that modify glucocorticoid tissue sensitivity and activation of peripheral cortisol metabolism.
- Hypoalbuminemia or reduced CBG can also decrease total fraction bound to cortisol in serum, resulting in lower total cortisol levels (whereas free cortisol may be normal or increased).

Critical Illness-related Corticosteroid Insufficiency

- Recommendations for diagnosis and management of corticosteroid insufficiency in critically ill adult patients by the international task force by the American College of Critical Care Medicine in 2008 state that AI is best diagnosed
- -by a maximum change in cortisol level after ACTH-stim of <9 ug/dl
- -or a random total cortisol level <10 ug/dl

Critical Illness-Related Corticosteroid Insufficiency in Patients with Cirrhosis and Variceal Bleeding

Background & Aims: To assess whether adrenal insufficiency occurs in patients with cirrhosis with variceal bleeding

Methods: 20 cirrhotic patient with variceal bleeding were evaluated using 1ug of ACTH (low-dose, short synacthen test/LDSST) or with 250 ug of ACTH (conventional dose, short synacthen test/SST). Control group included 60 stable cirrhotic patients and 14 healthy volunteers

Results:

-All healthy volunteers had normal results from LDSSTs and SSTs.

-Patients with variceal bleeding had higher medial baseline concentrations of cortisol (15.4 ug/dl) than stable cirrhotic patients (8.7 ug/dl) or healthy volunteers (10.1 ug/dl)

-Patients with variceal bleeding had higher median peak cortisol than stable cirrhotic patients (SST results of 32.7 ug/dl versus 21 ug/dl)

Subanalysis of patients with albumin levels>2.5 g/dl did not change results

Conclusions: Cirrhotic patients with variceal bleeding have AI. Despite higher baseline cortisol and subnormal delta max values, they did not have adequate response to stress, and therefore had critical illness-related corticosteroid insufficiency.

Triantos, C., Marzigie, M, Fede, G. et. al. Critical Illness-Related Corticosteroid Insufficiency In Patients with Cirrhosis and Variceal Bleeding. Clinical Gastroenterology and Hepatology 2011;9:595-601.

Adrenal Insufficiency in HIV

- In patients with HIV, AI is known complication although estimates of prevalence and severity vary.
- Patients with AIDS are considered to be high risk for both primary or secondary adrenal insufficiency.
- Cause-primary adrenal infections including CMV, Mycobacterium avium-intracellulare (MAI), TB, cryptococcus, histoplasmosis, blastomycosis, toxoplasmosis, PCP or maliginancies including Kaposi Sarcoma and non-Hodgkins Lymphoma
- Secondary adrenal insufficiency can be caused by CMV or toxoplasmosis in the pituitary gland
- Anti-adrenocortical antibodies have been detected in patients with AIDS

Medications used in the treatment of HIV or its complications that may affect pituitary or adrenal gland function

Medication	Intended clinical use	Endocrine dysfunction	Mechanism of action
Corticosteroids	Anti-inflammatory (eg, adjunctive use in *Pneumocystis carinii* pneumonia)	Exogenous Cushing's syndrome; glucocorticoid deficiency upon discontinuation; hypogonadism	Suppresses hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-gonadal (HPG) axes
Interferon-α (IFN-α)	Treatment of co-infection with Hepatitis C	Panhypopituarism	Immune-mediated
Ketoconazole	Anti-fungal	Adrenal insufficiency; hypogonadism	Impairs steroid hormone synthesis
Megestrol acetate	Appetite stimulant	Cushing's syndrome (rarely); hyperglycemia; hypogonadism; glucocorticoid deficiency upon discontinuation	Intrinsic glucocorticoid-like and progestational activity
Opiates	Analgesic	Impaired cortisol response to ACTH stimulation; hypogonadism	Alterations in HPA & HPG axes
Protease inhibitors (PIs)	Anti-retroviral	Hyperprolactinemia	May stimulate lactotrophs directly or inhibit metabolism of other medications
Ritonavir	Anti-retroviral	Exogenous Cushing's syndrome (with concomitant use of inhaled fluticasone)	Effects on hepatic cytochromes and drug metabolism
Rifampin	Antibiotic and anti-mycobacterial agent (eg, tuberculosis)	Adrenal insufficiency	Increases metabolic clearance of hormones
Sulfonamides	Antibiotic	Hyporeninemic hypoaldosteronism	Interstitial nephritis

Courtesy of Melissa Weinberg, MD and Morris Schambelan, MD.

Adrenal Insufficiency in HIV/AIDS

- Studies examining adrenal function in HIV patients revealed normal or elevated basal cortisol levels, whereas ACTH levels have been reported as high, normal, or low.

- Autopsy study of 41 patients with AIDS, 80% were found to have adrenal cortical necrosis of as much as 70% of the adrenal mass but only 2 patients were tested pre-mortem with ACTH stim (1 of 2 pts had abnormal test and the patient with abnormal test had <10% involvement of the adrenal cortex at autopsy and normal pigmentation)

- Several case reports in the literature have described patients with AIDS with clinical features suggestive of adrenal insufficiency, but their ACTH stimulation tests were normal. Repeat testing confirmed dx of AI and further testing with insulin tolerance test or overnight metyrapone test revealed secondary adrenal insufficiency in other patients.

Smolyar, D, Tirado-Bernadini R, Landman R et. Al. **Comparison of 1-micro g and 250-micro g corticotropin stimulation tests for the evaluation of adrenal function in patients with acquired immunodeficiency syndrome.** Metabolism. 2003 May;52(5):647-51.

- **Background:** Many patients with acquired immunodeficiency syndrome (AIDS) have symptoms suggestive of adrenal insufficiency, but a normal 250- micro g corticotropin (ACTH) stimulation test. We compared the results of 1- micro g and standard 250- micro g ACTH stimulation tests in patients with AIDS.

- **Methods:** Each patient was studied on 2 separate days. On day 1, 1 micro g ACTH was given intravenously at 8 am after an overnight fast and serum cortisol levels were measured at baseline, and 30 and 60 minutes after ACTH infusion. On day 2, the procedure was repeated with 250- micro g ACTH. An absolute peak cortisol value of > 18 micro g/dL and an increment of 7 micro g/dL or more from baseline constituted a normal response.

Smolyar, D, Tirado-Bernadini R, Landman R et. Al. **Comparison of 1-micro g and 250-micro g corticotropin stimulation tests for the evaluation of adrenal function in patients with acquired immunodeficiency syndrome.** Metabolism. 2003 May;52(5):647-51.

- **Results:** Among 31 patients, 16 (52%) had discrepant results: 14 (45%) had subnormal responses to 1 micro g ACTH but normal responses to 250 micro g ACTH (group 1); 2 (6%) had normal responses to 1 micro g but subnormal responses to 250 micro g (group 2) ACTH; 6 patients (19%) had concordant abnormal responses (group 3); and 9 (30%) had concordant normal responses (group 4).
- Eight patients of group 1 underwent a confirmatory insulin tolerance test (ITT); 4 of these patients had abnormal responses to ITT.

- **Conclusion:** We conclude that discrepancies between the 1- micro g and the 250- micro g ACTH stimulation tests are common in patients with AIDS, with the likelihood of agreement with the "gold standard" ITT of only 50% for each test in our sample of patients. Larger studies are needed to further evaluate the use of these tests in patients with AIDS.

Recommendations

- Start hydrocortisone 100 mg IV q8h

Hospital Course

- That night of consult, patient became hypotensive with diffuse abdominal pain
- Transferred to ICU
- Given 500 cc normal saline, albumin, cefepime for empiric SBP treatment
- Developed UGI bleed from esophageal varices, requiring multiple units of prbcs and FFP
- Intubated for airway protection; Had esophageal varices banded
- Serum Na trend: 121->126->129->133->140
- Extubated but developed hepatic encephalpathy and had to be reintubated for mental status
- Scheduled for liver transplant, but cancelled due to poor condition of donor liver
- Hospital course further complicated with E.coli bactermia, renal failure requiring CVVHD
- Family meeting held due to worsening liver failure, renal dysfunction, overall poor prognosis and decision was made to change treatment goals to comfort care.
- Patient extubated, morphine gtt started, and he passed away with family at bedside.

Take Home Points

- Liver failure can contribute to AI by increasing levels of endotoxin and impairing cholesterol synthesis.

- Critical Illness Related Adrenal Insufficiency is defined by

-by a maximum change in cortisol level after ACTH-stim of <9 ug/dl

-or a random total cortisol level <10 ug/dl

- Adrenal insufficiency is common in patients with liver disease not only during acute critical illness (ie. Sepsis, shock, and variceal bleeding), but also during stable cirrhosis.

- Patients with HIV/AIDS are considered to be high risk for both primary or secondary adrenal insufficiency.

- HIV/AIDS patients with suspected adrenal insufficiency who have normal ACTH stim tests should undergo further testing for secondary adrenal insufficiency if clinically warranted.

References

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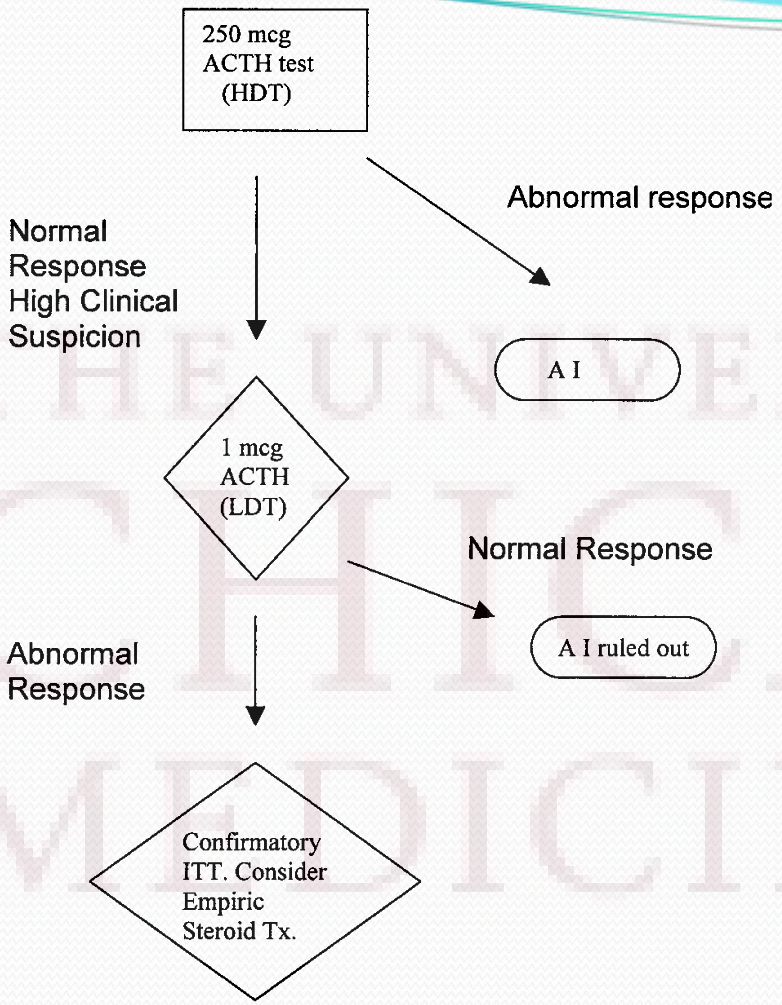

Fig 5. A proposed algorithm for evaluating a patient with AIDS for possible adrenal insufficiency. ITT, insulin tolerance test; AI, adrenal insufficiency.

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