Endocrine Emergencies

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Disclosure of Financial Relationships

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None

Objectives

- Discuss the diagnosis, prognosis, and management of three Endocrine emergencies
- Myxedema Coma
- Thyroid Storm
- Adrenal Crisis

Case #1

- 62 yo F with altered mental status
- Brought to ED by son
- Medical history is largely unknown but son thinks she is taking levothyroxine therapy and a blood pressure medication

Case #1 – Physical Examination

- Temp 91.0 F, HR 48, BP 104/56, RR 12, wt 98kg, BMI 32
- Gen: Caucasian female, somnolent but arousable.
- HEENT: Scalp hair thin. Periorbital edema bilaterally, sclera anicteric. Eyebrows notable for loss of lateral third. +Macroglossia
- Neck: no obvious thyroid abnormalities but exam is limited because patient is supine

Case #1 – Physical Examination

- CV: HR in mid 40s, regular rhythm. No murmurs appreciated
- Lungs: Mildly decreased breath sounds bilaterally
- Abd: soft, nontender, nondistended
- Ext: 1+ BLE edema, nonpitting
- Skin: dry, coarse. Brittle nails.
- Neuro: Bicep reflexes are 1+ with a significant delay in the relaxation phase

Case #1 - Labs

- Na 127, glucose 60, BUN 30, Cr 1.4 (unknown baseline)
- Hgb 10.9, WBC 12, plt normal
- UA concerning for possible UTI, Ucx sent

Diagnosis of Myxedema Coma Pearls

- Three essential elements for diagnosis, confirmed by laboratory testing
  - Altered mental status
    - Coma unusual; generally disorientation, extreme lethargy
  - Defective thermoregulation
    - Defective hypothalamic function and inability to produce heat
  - Precipitating event or illness is common
    - Pulmonary and urinary tract infections common

Endocrine Reviews 2003;4:137

- 2014: Diagnostic Scoring System proposed based on retrospective chart review of 21 patients
  - 14 w/ myxedema coma
  - 7 initially classified as myxedema coma but reviewers disagreed w/ diagnosis (4 based on labs, 3 based on no mental status changes)

Endocrine Practice 2014;20:808

Diagnostic Criteria of Myxedema Coma

– Scores given based on the following:

Temp (>35, 32-35, <32)	**CV dysfunction:** - **Bradycardia (absent, 50-59, 40-49, <40)** - **Other EKG changes (QT prolongation, low voltage, BBBs, nonspecific ST-T changes, heart blocks)** - **Pleural or pericardial effusions** - **Pulm edema** - **Cardiomegaly** - **Hypotension**
CNS Effects (absent, somnolent/lethargic, obtunded, stupor, coma/seizures)	
GI findings (anorexia/abdominal pain/constipation, decreased motility, paralytic ileus)	**Metabolic disturbances (Hyponatremia, Hypoglycemia, Hypoxemia, Hypercarbia, Decreased GFR)**
Precipitating event (absent, present)	

Endocrine Practice 2014;20:808

Prognosis and Etiology of Myxedema Coma

- Mortality rates are 25-60%
- Estimated incidence of 0.22 million per year
- Infections and septicemia are the most common precipitating events; Poor adherence to outpatient levothyroxine often contributes
- 95% of patients have primary hypothyroidism, about 5% central hypothyroidism

J Thyroid Research 2011;doi:10.4061/2011/493462

Back to Case #1

- TSH and T4 are pending to evaluate for hypothyroidism and you are concerned the patient has myxedema coma.
- You want to start IV thyroid replacement as soon as possible BUT what do you need to evaluate first?

Adrenal Insufficiency

- Treatment with thyroid replacement in someone with adrenal insufficiency can precipitate an adrenal crisis!
- Ideally, send cortisol level prior to empiric steroid therapy if possible. Consider cosyntropin stim test if able to obtain post stim cortisol level.
- Start IV glucocorticoid replacement prior to IV levothyroxine

Myxedema Coma Treatment

- 1) IV high dose glucocorticoid therapy
  - Hydrocortisone 100 mg x 1, then 50 mg IV q 6hr or 100 mg IV q 8 hr
- 2) After steroids, give IV thyroid replacement:
  - Combo T4/T3: Load IV LT4 200-400 mcg followed by 1.6 mcg/kg/day; Load T3 5-20 mcg followed by 2.5 -10 mcg q 8 hrs. T3 discontinued once pt is stable.
    - T4 only: Load IV LT4 300-500 mcg bolus to saturate pool, then 50-100 mcg daily.
    - T3 only: 10-20 mcg, followed by 10 mcg q 6hr for 1-2 days
    - If IV is not available use PO. Gut wall edema and/or gastric atony may impair PO absorption.

UpToDate accessed 2/3/17; last updated 6/3/15
J Thyroid Research 2011;doi:10.4061/20111/493462

Myxedema Coma Treatment

- Need ICU monitoring due to risk of respiratory failure and/or hypotension
- Hypotension may be due to volume depletion but may also respond to thyroid hormone replacement
  - May need transient vasopressor support
- Passive rewarming (blanket) preferred
  - Active rewarming can cause vasodilation and shock

UpToDate accessed 2/3/17; last updated 6/3/15

Case #2

- 73 yo AAF w/ h/o hyperthyroidism, s/p discontinuation of propylthiouracil (PTU) 7 days ago for a planned thyroid uptake and scan.
- Presents w/ a 2 day h/o lethargy, slurred speech and low grade temp.
- N/V on day of admission

Case #2 - Physical Exam

- HR 120-170 on telemetry, temp 100.5, very lethargic
- HEENT: +stare and lid lag; no proptosis or chemosis; sclera anicteric
- Neck: thyroid enlarged and nodular, no bruit
- CV: Reg rhythm but tachycardic
- Resp: Fair respiratory effort, no crackles
- Ext: No c/c/e
- Neuro: Brisk reflexes, fine tremor present
- What are you concerned about?

Thyroid Storm – Clinical Presentation

- Thyrotoxicosis features are accentuated:
  - Thermoregulatory dysfunction
    - Low grade temp → temp >104 (sweating can lead to insensible fluid loss)
  - Cardiovascular
    - Tachycardia → HR >140; afib; CHF
  - CNS disturbance
    - Agitation → delirium, psychosis, extreme lethargy → seizure coma
  - N/V/D → jaundice
  - Precipitant history usually present

Thyroid 2011;21:593; J Int Care Med 2015;30:131
Endocrinol Metab Clin North Am 1993;22:263

Precipitants

- Thyroid surgery (previously the most common precipitant, but rare now), Vigorous thyroid manipulation
- Withdrawal of antithyroid drug therapy
- Radioiodine therapy (rare), Iodinated contrast dyes
- Nonthyroidal surgery, Trauma
- Infection, CVA, PE, Parturition, DKA, Hypoglycemia, Burn, MI
- Thyroiditis, metastatic thyroid cancer, struma ovarii, molar pregnancy
- Emotional stress, intense exercise
- Meds: anesthetics, salicylates, amiodarone, pseudoephedrine, IFN, acute ingestion of high doses of LT4

Thyroid 2011;21:593; J Int Care Med 2015;30:131

Atypical presentations

- Apathetic hyperthyroidism
  - May present with apathy, obtundation, cardiac failure
  - Elderly or those with nonthyroidal illness may not have typical signs and symptoms of thyrotoxicosis, which can lead to delay in diagnosis

J Int Care Med 2015;30:131

Laboratory Testing

- No definitive serum T4 or T3 cutoff to differentiate storm (from thyrotoxicosis without crisis)
- T3 may not appear as high as expected in critically ill patients because of decreased ability to convert T4 to T3
- Common abnormalities: leukocytosis (+/- infection), elevated BUN, elevated transaminases, hyperbilirubinemia, hypercalcemia (high bone resorption), hyperglycemia (increased catecholamines and gluconeogenesis, inhibition of insulin release)

J Int Care Med 2015;30:131

Treatment of thyroid storm

- Beta-adrenergic blockade
- Antithyroid drug therapy (thionamides)
- Iodine
- Glucocorticoids
- Other: Lithium, cholestyramine, physical removal
- Supportive treatment: APAP, cooling blankets, IVF, resp support, ICU monitoring
- Avoid salicylates – Can increase FT4 by decreasing binding to T4 binding globulin

Thyroid 2011;21:593, J Int Care Med 2015;30:131

Beta Blockade

- Hyperthyroidism - increased # beta-adrenergic receptors, likely responsible for many symptoms
- Propranolol – Used in storm because it blocks T4 to T3 conversion in high doses
  - PO 60-80 mg q 4 hrs
  - Can use IV for faster effect (0.5 to 1.0 mg slow IV push then 1-2 mg at 15-min intervals while monitoring on telemetry
- Alternative (i.e. if borderline BP): Esmolol IV
  - Bolus 0.25-0.5 mg/kg, followed by infusion 0.05-0.1 mg/kg/min

Thyroid 2011;21:593; J Int Care Med 2015;30:131

Thionamides – PTU and methimazole

- Block new thyroid hormone synthesis within 1-2 hours
  - Inhibit thyroid peroxidase, key enzyme in formation of T4 and T3 from thyroglobulin
- PTU favored in storm (inhibits peripheral conversion of T4 to T3).
  - +/-Load 500-1000 mg PO, then 200-250 mg q4hr
- Methimazole: 60-80 mg/day, in divided doses
- Usually PO, but can be suppository or retention enema
    - Methimazole available IV in Europe; Can be prepared by dissolving methimazole powder in normal saline (in sterile fashion) if needed.

Thyroid 2011;21:593; J Int Care Med 2016;30:131
Thyroid 2006;16:691

Side effects of thionamides

- Agranulocytosis (ANC <500)
  - Reviews from Taiwan and Japan
    - 5653 hyperthyroid pts treated w/ antithyroid drugs 1987-97
      - 13 (0.23%) developed life-threatening infections (leukopenia in 1-5% pts treated w/ antithyroid medications)
      - **Presentations: fever 92%, sore throat 85%**
      - 6 had +BCx: Pseudomonas 3, E coli 1, S aureas 1, Capnocytophaga 1
      - Reviewed lit: gram neg bacilli incl Klebsiella and P aeruginosa were the most common pathogens in clinical isolates; *thus broad-spectrum abx should cover pseudomonas*
    - 754 cases of ATD-induced agranulocytosis reported over 30 years
      - >70% of patients developed agranulocytosis within 60 days; nearly 85% within 90 days

QJMed 1999;92:455; JCEM 2013;98:4776

Side effects of thionamides

- Vasculitis, ANCA associated
- Hepatotoxicity
  - PTU - FDA has black box warning
  - Methimazole - More of a cholestatic picture

- Providers need to monitor labs and symptoms possibly related to side effects
- Patient needs to notify provider:
  - Fever and sore throat – check blood count
  - Rash – r/o vasculitis.
  - Abdominal pain, darkening of urine, itching, nausea – check LFTs

Iodine-Containing Solutions

- Block release of T4 and T3 from the thyroid gland
  - Inhibit proteolytic release of T4 and T3 from thyroglobulin
- Block new hormone synthesis
  - Inhibit organic binding of iodide to TG in the thyroid (Wolff-Chaikoff effect)
  - Transient decrease in thyroid hormone synthesis
  - Escape phenomenon eventually occurs, usually within 2-4 wks, and thyroid hormone synthesis resumes

Thyroid 2011;21:593; J Int Care Med 2016;30:131
Endocrinology 1999;140:3404

Iodine

- SSKI (saturated solution of potassium iodide)
  - 5 drops (0.25mL or 250 mg) PO every 6 hours
- Lugol's solution 8 drops every 6 hours
- **Do NOT administer until one hour after antithyroid medication has been given (to prevent iodine from being used as substrate for new thyroid hormone synthesis)**
- Would recommend Endocrine consultation in anyone you are considering SSKI

Thyroid 2011;21:593

Glucocorticoids

- Inhibit T4 to T3 conversion
- Prevent AI
  - HPA axis may be impaired in thyrotoxicosis with decreased adrenal reserve (subnormal adrenal response to ACTH)
- Hydrocortisone
  - 300 mg IV load, then 100 mg IV q 8 hours
- Dexamethasone is alternative drug

Thyroid 2011;21:593, J Int Care Med 2015;30:131
Eur J Endocrinol 2000;142:231

Other Treaments

- Cholestyramine
  - Entero-hepatic circulation of thyroid hormones is increased in thyrotoxic state
  - Thyroid hormone is conjugated in liver, and conjugation products are excreted in bile whereas free hormones are released, reabsorbed and circulate
  - Cholestyramine binds conjugation products, thus promoting excretion and lowering thyroid hormone levels
  - 1-4 g BID
- Physical removal
  - Plasma Exchange – During exchange, TBG w/ bound thyroid hormone is removed; colloid replacement supplies open binding sites for circulating free thyroid hormone
  - Transient as as adjunct to medical therapy or prior to surgery

Thyroid 2011;21:593, J Int Care Med 2015;30:131

Other Treatments

- Lithium
  - Impairs thyroid hormone release and blocks new thyroid hormone synthesis (Inhibits coupling of iodotyrosine residues)
  - Alternative if pt has h/o iodine induced anaphylaxis
  - Initial dose is 300 mg q 6-8 hrs, then adjust to maintain serum lithium levels <1mEq/L
  - Significant renal and neuro toxicity limits its usefulness

J Int Care Med 2015;30:131

Back to Case #2

- History, PE and lab evaluation are concerning for thyroid storm.
- She has already received one dose of IV propranolol, APAP and was started on IVF.
- She is admitted to the ICU.

In addition to continuing propranolol therapy, what would you add to her regimen?

- A) PTU 250 mg q 4 hr
- B) PTU 250 mg q 4 hr; HC 100 mg q 8 hr
- C) PTU 250 mg q 4 hr; HC 100 mg q 8 hr; SSKI 5 drops q 6 hr one hour after PTU
- D) Plasma exchange
- E) No thyroid-specific therapy until diagnosis is confirmed

Thyroid pearls – Common meds that affect thyroid levels

- Heparin (IV, SQ) – falsely elevates FT4 and FT3
  - If TSH normal, consider checking total thyroid levels
- Estrogen – Increases TBG, thus increases thyroid requirements
  - Pregnancy – Pts need increase in LT4 upon confirmation of pregnancy; multiply TOTAL T4 ref range by 1.5 for pregnancy
  - Menopause and OCPs change LT4 requirements
- Steroids – Suppress TSH; Block T4 to T3 conversion
- Amiodarone – decreases conversion T4 to T3 (thus elevated FT4 w/ low or low-nl T3 and normal TSH)

Case #3

- 58 yo M w/ CKD3, CAD, CHF w/ EF 30%, T2DM, chronic back pain for which he takes high doses of opioids, presents with syncopal episode and hypotension (85/50). He has had 2 days of N/V/D prior to admission.
- Following volume resuscitation, BP is improved (104/62, however, he still has mild orthostasis
- Because of his h/o chronic narcotics, you would like to evaluate for adrenal insufficiency (AI)
- What would be an appropriate initial study?

AI Diagnostic testing

- 8am cortisol can be used to screen for AI if pt is stable and evaluation can wait until the next morning
- 8am Cortisol <3mcg/dL suggests cortisol deficiency. >15 excludes the diagnosis.
- Endocrine Society guidelines recommends cosyntropin stimulation test (250 mcg) for confirmation of AI in most patients
- Measuring ACTH will provide insight into primary vs. secondary AI
- Cannot measure cortisol when taking steroids other than dexamethasone (cross react with assay)

JECM 2016;101:364

Case #4

- 36 yo F w/ T1DM, hypothyroidism, AI, presents to ED with extreme fatigue, weakness, abdominal pain, N/V, inability to take POs including meds
- BP 92/54, P 115 lying
  - 72/44, P 138 standing
- Labs demonstrate sodium 127, K 5.7, glucose 65, no DKA, corrected calcium 10.8.

Case #4 – Treatment of Adrenal Crisis

- Hydrocortisone 100 mg IV x 1, followed by 50 mg IV q 6 hrs (or continuous infusion 200mg/24 hr)
- Volume resuscitation
- Once stabilizes, wean steroids to lower doses IV then to PO.
  - Maintenance doses
    - HC 15-25 mg/day in 2-3 divided doses
    - Cortisone acetate 20-35 mg/day in 2-3 divided doses
    - Prednisolone (3-5 mg/day)
  - Fludrocortisone required if aldosterone deficiency

JECM 2016;101:364; Endocrine 2017;55:336

Patient Education

- Sick day rules
- Steroid emergency card or medical alert identification
- Glucocorticoid injection kit and education on use
- Follow with Endocrine at least once per year

JECM 2016;101:364; Endocrine 2017;55:336

THANK YOU FOR YOUR PARTICIPATION!

- Questions?

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