Fall and long lie: Diagnostic dilemma

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Case vignette

- 75Y, Male, Black British
- Lives with nephew, TDS POC, day time alone in-between care visits
- PC: Found fallen on the floor
- PMH: L/MCA infarction with residual mild R/weakness, post-stroke epilepsy (Hx of status epilepticus 6 months ago), bilateral LL eczema, constipation, BPH, HTN
- DHx: Levitiracetam 500mg BD, emollient cream, Ramipril 2.5mg OD, clopidogrel 75mg OD, atorvastatin 20mg ON, Tamsulosin 400 microgram OD, docusate 200mg BD and senna 15mg ON
- Baseline functional level:
  - 2 months ago, used to go to the nearest convenience shop to buy newspapers and cigarettes using a tripod, but stopped following a near fall associated with dizziness, not report to the hospital. Assistance is needed in cooking, laundry and housekeeping
  - Independent in all BADL until 4 weeks before
  - Need assistance of one to the toilet/ bathing last 4 weeks, needed prompting and assistance for all BADL last 1 week

History of Presenting Complain:

Hx from carer and nephew:

-Found fallen on the floor by carer next to the bed around 6.30 pm, last seen by the carer during lunch around 1pm, fall is unwitnessed

-No recollection, patient is drowsy, tremulous and pants were wet: carer was concerned about a seizure and an ambulance was called

-Last 4 weeks gradually reduced mobility: struggling to get up from a seated position, poor balance on walking, getting tired easily, prefers to be in the bed sleeping all the time, no falls until today

-Lethargic, withdrawn, less talkative, poor memory, less eating and drinking

-Confused from time to time during last week

-Increased urine frequency, no dysuria, no haematuria. No fever/nausea/vomiting/cough/SOB

-Reviewed by GP (paramedics visited home) 5 days ago and started on nitrofurantoin for probable UTI (FBC/CRP non-exciting, urine pus cells positive)

-Bowel not opened for 1 week before GP review, only minimal response to increased laxatives

-Some slurring of speech over the last 4 days, but no FAL weakness

-No hx of alcohol dependence/ drug abuse or withdrawal

-No hx of abnormal movements noted apart from tremulousness

Assessment by ambulance paramedics:

A: Patent

B: RR 18, **SpO2 82%**

C: **PR 55, regular, BP 99/75,** cold peripheries, CRFT 3sec

D: Drowsy but responds to voice, confused, moving all 4, CBG: 4.5

E- Temp 34.3C, Bilateral lower leg eczema, LL odema, wet pants, central heating and an additional portable heater next to his bed

Secondary survey: no external injuries, no spinal tenderness including cervical spine, no evidence of deformities, all the joints passive movements without any pain

Actions: 15L NRM O2, wet cloths changed, covered with blankets, IVF started, transferred the patient immediately to ED

ABG performed immediately after admitting to ED due to low saturation despite 80% O2: PH 7.32, PaO2 21 (with 15L NRB), PaCO2 5.2, sO2 99%, HCO3 18, Lac 3.4 mmol/l, Glu 4.2 mmol/l, Urea 15.8 mmol/l, Na 129 mmol/l, K 5.7 mmol/l, Cl- 105 mmol/l

Further assessment at ED:

Averagely built

Pale, not icterus, dry mucosa++, no tongue bite evident

eczema in bilateral legs associated with dry skin

leg odema up to knees

No bruises or lacerations, pressure areas intact

- CNS: GCS: 11/15 (M 5, V3, E 3)

No neck rigidity

slurred speech

eye movements are full range, no nystagmus, no facial asymmetry

Hands are tremulous, but tone is normal, Moving all 4 symmetrically, at least power 3/5, reflexes +, plantar down

Sensory assessment not reliable, Detailed cerebellar assessment not possible due to confusion

- MSK- no spinal tenderness, no hip or pelvic tenderness, all joint movements not painful
- Abdomen: SNT, bowel sounds present, no FF, catheterized and draining clear concentrated urine, DRE: hard stool in rectum
- CVS: PR 52, regular, dual rhythm, no murmurs
- RS: Normal

Acute issues:

1. Fall with a possible long lie

multifactorial: reduced mobility over weeks, delirium, ? Seizure, ? Underlying infection, polypharmacy, hx of dizzy episodes, alone in-between care visits

2. Hypothermia: DDx- Long lie associated/ cold sepsis/ to rule out hypothyroidism

3. Dehydration

4. Metabolic derangements

a. Hypovolaemic hyponatremia: poor intake/ ?SIADH/ Drug-induced/ ?hypothyroidism

b. Hyperkalaemia

c. Lactic acidosis: ? Sepsis/ ? Seizure induced

5. Bradycardia and marginal blood pressure

6. ? UTI

7. ?Suspicion of seizure

8. Constipation

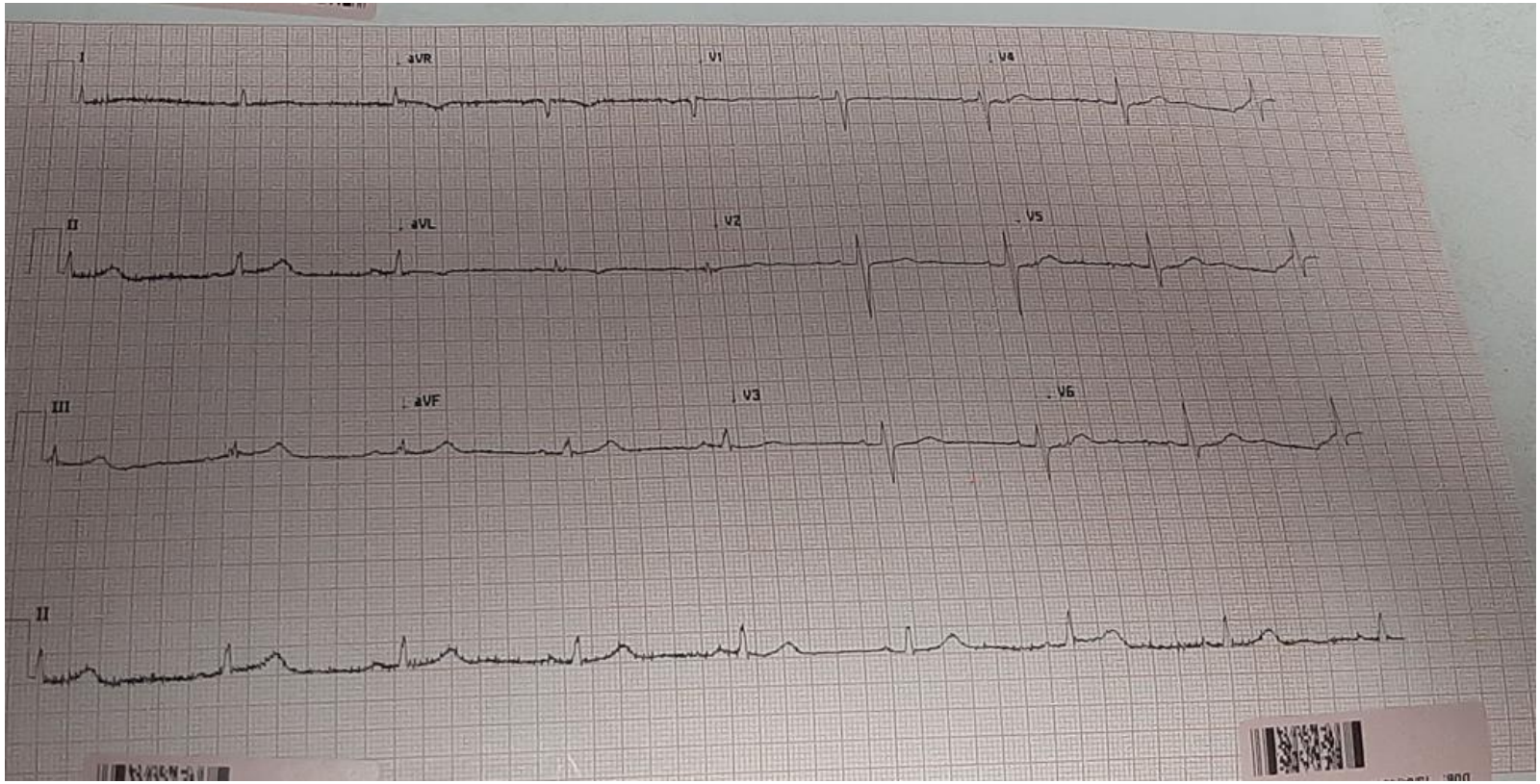
9. Reduced functional level over weeks

DDx: subacute stroke/autoimmune encephalitis/ meningo-encephalitis/ ?hypothyroidism

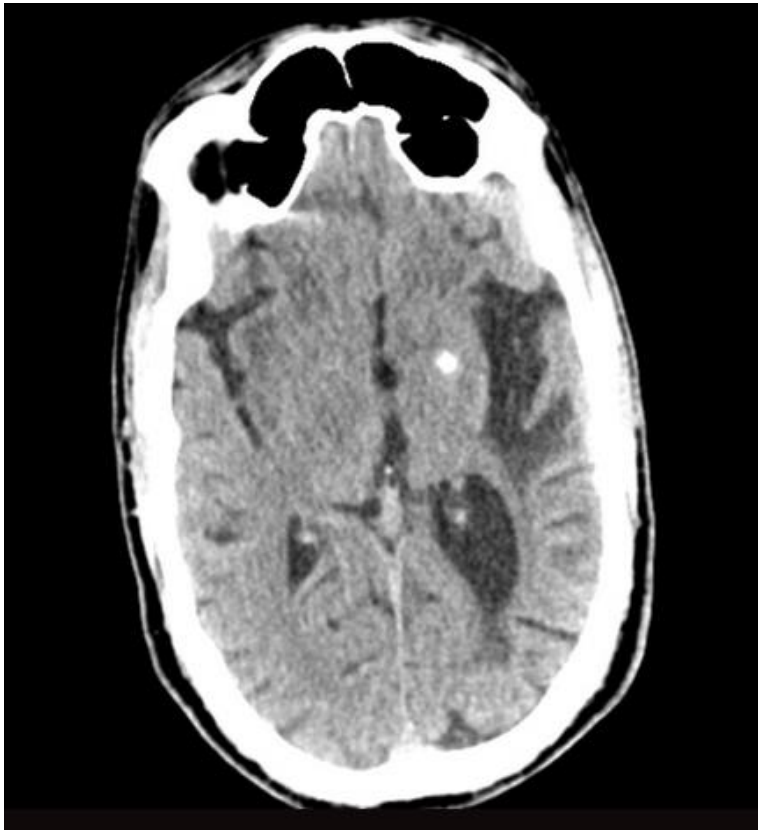
10. Delirium contributed by the above

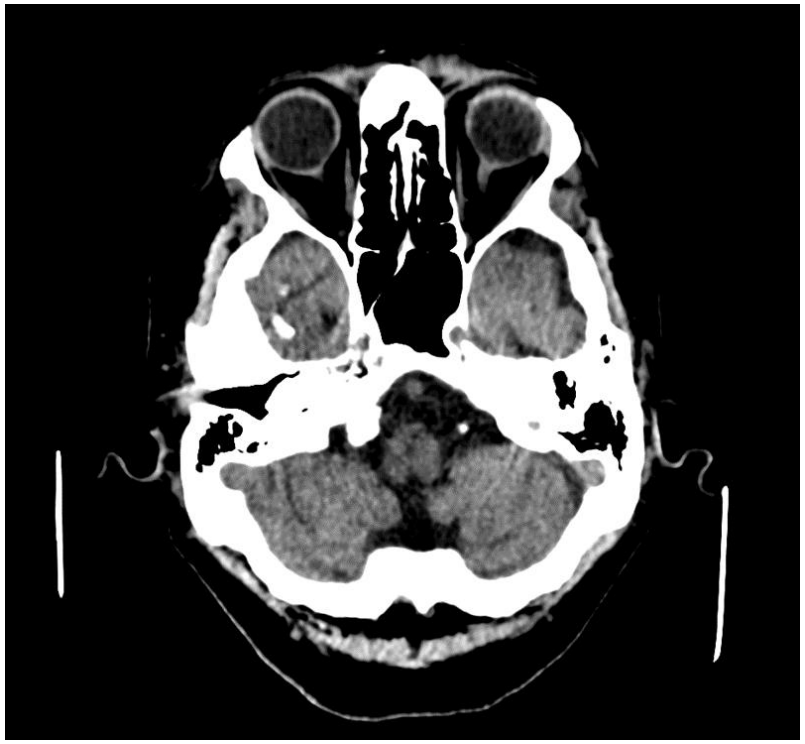
Investigations

- ECG



- CTH





- **Basic bloods**

FBC: WCC 10.8, Neut 8.2, Hb 109, MCV 102, Plt 160

CRP: 22

Creatinine kinase: 560 U/L

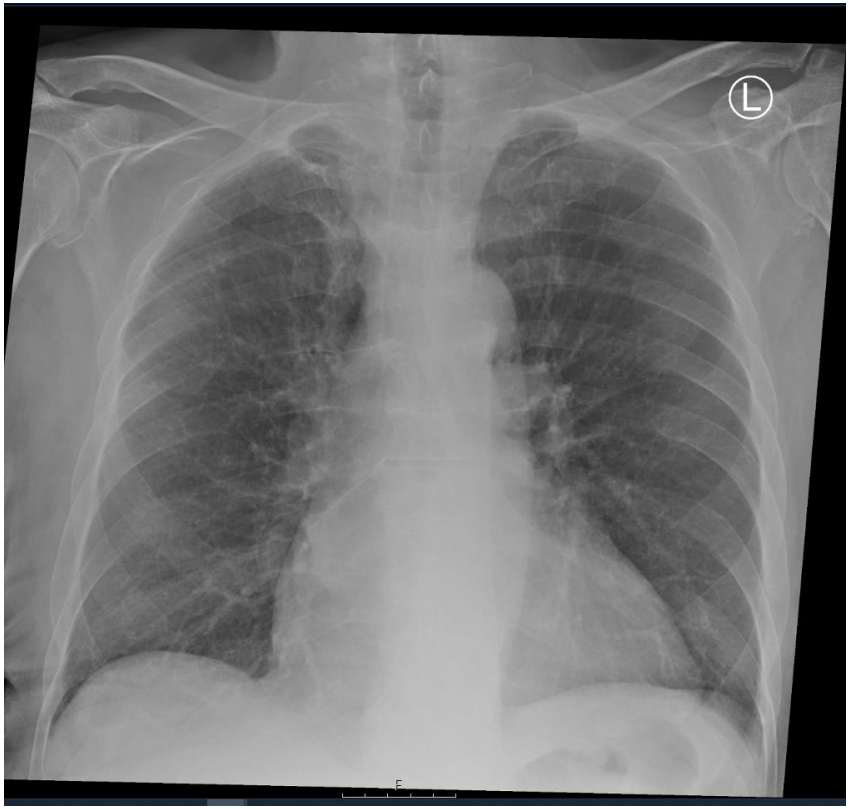
S. creatinine: 188 (baseline 105), eGFR

Na: 127, K: 5.6

LFT: albumin 28, AST/ALT: 85/99, ALP/ GGT: within normal limits

- Urine dip: positive for nitrite and pus cells, await urine microscopy and culture sensitivity

- CXR



Further issues identified after basic investigations

1. AKI with rhabdomyolysis
2. Mildly elevated inflammatory markers with urine dip positivity (A/W urine MCS)
3. Macrocytic anemia
4. Mildly elevated transaminases

Immediate management carried out

- Re-warming with Bair Hugger and monitor temperature
- IV sodium chloride 1l over 1 hr, then over 4 hrs: to assess the fluid status and Na levels before further fluid prescription to decide the rate and type of fluids
- Blood cultures and IV Abx as per trust guidelines: IV amoxicillin and IV gentamicin
- IV hydrocortisone 100 mg stat was given due to the suspicion of adrenal insufficiency given electrolytes derangement, marginally low BP and low normal sugar levels
- TFT, random cortisol, serum osmolality, B12, folate level, Mg levels, bone profile: added on to the Ix
- Urine Na and U. osmolality to be sent
- Monitor vitals hourly, CBG 4 hourly, IP/OP monitoring
- Glycerol suppository stat, monitor bowels, if no response plan micro enema
- OT/PT assessment
- LP and csf studies to be decided following other pending Ix
- Observe for seizure activity
- Monitor inflammatory markers, renal and electrolytes, liver functions, creatinine kinase. Chare urine MCS and blood cultures
- VTE prophylaxis: enoxaparin 40 mg OD
- Treatment escalation plan: full escalation was decided considering his background functional level 4 weeks ago and the reversible factors underlying

Results of further investigations:

- Random cortisol level: 680 nmol/l
- TSH level: 89 mU/l (0.4-5.4)
- FT4 level: 0.98 pmol/l (7.9-14.4) , FT3 level: 0.1 pmol/l (3.8-6)
- Folate and B12: low folate, B12 normal
- Mg, Ca, Phosphate: normal
- Paired osmolalities and
  - Serum osmolality: 268 mOsm/kg
  - Serum Na: 127
  - Urine osmolality/ Urine Na: unfortunately not available

Further History and Examination:

- Further information from nephew and carer
  - More sleepy, always asking to check if the radiator is working, needing heating even in late summer. More prompting is needed to have a bath
  - Legs become heavy with odema
  - Marked difficulty to get up from a seated position
  - Unsteady on his feet
- Constipation is always has been a problem, with worsening severity, attributed to age
- Prominent proximal muscle weakness and slow relaxing reflexes were elicitable

Further Mx:

In Liaison with critical care consultant and endocrinologist:

- Admitted to the ICU for close monitoring
- Slow rewarming to avoid reflex hypotension due to peripheral vasodilation
- IV 200 micrograms of levothyroxine stat, IV levothyroxine 50 microgram following 2 days and converted to oral from Day 4
- IV hydrocortisone 100mg 8hrly continued for 48 hrs
- Rpt TFT on Day 2:
  - TSH level: 72 mU/l (0.4-5.4)
  - FT4 level: 3.7 pmol/l (7.9-14.4) , FT3 level: 1.3 pmol/l (3.8-6)

Unifying diagnosis

“Myxedema coma”

- Precipitated by: Urine infection and hypothermia in winter

Myxedema coma

- Myxedema coma is a misnomer!
  - i) Most patients *aren't* truly comatose (but they are generally delirious)
  - ii) Most patients don't have classic non-pitting edema (myxedema)
- The construct of “myxedema coma” sets clinicians up for diagnostic failure
- Rather than thinking about “myxedema coma”: we need to think about compensated vs decompensated hypothyroidism

Decompensated hypothyroidism

- Decompensated hypothyroidism may be conceptualized as *hypothyroidism causing organ failure*
- The first organ to fail is generally the brain. Thus, a clinical hallmark of decompensated hypothyroidism is *delirium/* deteriorating mentation

compensated hypothyroidism
(organs working)

- Fatigue
- Depression
- Cold tolerance
- Hoarseness

decompensated hypothyroidism
(organs failing)

- Delirium
- Hypothermia
- Bradycardia, shock
- Hypoglycemia

Physiologic stress, e.g.:

- Sepsis
- Cold exposure
- Surgery, Burns, Trauma
- Med nonadherence

Recognition of clinical syndrome

- **core features that may help suggest decompensated hypothyroidism:**

(1) Altered mental status:

  - Usually *not* frankly comatose, most patients have hypoactive delirium
  - Rarely, may see an activated form known as “myxedema madness”

(2) Presence of one of the following two cardinal features:

  - Hypothermia (may be severe)
  - Bradycardia

- **may also see:** Features of precipitating event, Hypoglycemia, Hyponatremia, Hypoventilation, Reduced bowel & bladder motility
- **clues to the diagnosis of hypothyroidism:** Any history of prior thyroid disease (either hyper- or hypothyroid), Thyroidectomy scar or goiter, Myxedema (Non-pitting edema of hands/ankles/ face, Hoarseness, macroglossia), Hair loss, loss of outer third of the eyebrows, Cold intolerance

Precipitating factors for “myxedema coma”/decompensated hypothyroidism

- Infections: urinary tract infection, pneumonia, viral infections, influenza, etc.Decompensated hypothyroidism can mask may features of sepsis (including fever and leukocytosis).
- Burns, carbon dioxide retention, and trauma
- Hypothermia (myxedema coma is more common in the winter: 90% of cases).
- hypoglycemia, Hypoxemia
- cerebrovascular accidents
- Drugs: amiodarone, lithium, sedatives, tranquilizers, anesthetics, opioids, phenytoin, rifampin, diuretics, beta-blockers, anti-TNF therapy, Some iodinated contrast dyes

(given the slow drug metabolism in patients with hypothyroidism, these patients have a risk of an overdose of anesthetics and tranquilizers)

- Congestive heart failure
- Gastrointestinal bleeding
- Surgery (given the effect on pituitary-thyroid axis with decrease thyroid hormones secretion after surgery in response to stress)

Other manifestations in “myxedema coma”/decompensated hypothyroidism

Neurological Manifestations:

- Typically patients do not present with coma, especially in the early phase, but they present with lethargy, delirium. The course is commonly a slow progression to coma
- Other findings may include depression, disorientation, psychosis, slow mentation, paranoia, and poor recall
- Decrease deep tendon reflexes
- Proximal myopathy
- Seizures can occur, including status epilepticus (potentially exacerbated by hyponatremia)
- LP can show increased pressure and high protein count, attributable to increased meningeal permeability and cerebral blood flow and a decrease in metabolism
- non-specific EEG changes can occur

Cardiac Manifestations:

- Diastolic hypertension followed by hypotension
  - Diastolic hypertension is one of the cardiovascular compensatory mechanisms in hypothyroidism. (Hypothermia and decreased respiratory drive cause peripheral vasoconstriction)
  - When the diastolic blood pressure starts *falling*, this may be a poor sign
  - Decreased myocardial contractility and reduced cardiac output, bradycardia, pericardial effusion can all lead to hypotension (late finding)
- Bradycardia is a common manifestation
- arrhythmia, and heart block
- Pericardial effusion due to the accumulation of fluid rich in mucopolysaccharides
- Fatal arrhythmias are important to recognize in Myxedema and chronic hypothyroidism
- Myocardial infarction is important to rule out as aggressive T4 replacement may increase the risk of myocardial infarction
- **EKG findings:** Sinus bradycardia (most often), bundle branch blocks, and complete heart blocks. flattened T waves , QTc may be prolonged, potentially leading to Torsades de Pointes. Low voltage complexes due to pericardial effusion

Respiratory Manifestations

- Hypoventilation due to impaired hypoxic and hypercapnic ventilatory response and the associated diaphragmatic muscle weakness
- The primary cause of coma in myxedema appears to be due to respiratory depression due to decreased response to hypercapnia
- Also, swelling of the tongue and vocal cords leads to obstructive sleep apnea contributing to respiratory failure
- Reduction in tidal volume due to pleural effusion or ascites

Renal and Electrolyte Manifestations

- Typical findings are hyponatremia and decreased glomerular filtration rate
  - Hyponatremia occurs mainly due to decreased water transport to the distal nephron. Other causes can be an increase in antidiuretic hormone (ADH)
  - Serum osmolality is low. Urinary sodium excretion is increased or normal. Urinary osmolality elevates relative to plasma osmolality
  - Hyponatremia is also a key factor in the patient's altered mental status and development of a coma
  - Mild hyponatremia will resolve with thyroid supplementation.
- Acute kidney injury may result from hypoperfusion and possibly also from rhabdomyolysis
- Patients may also have bladder atony causing urinary retention

Gastrointestinal Manifestations

- commonly causes constipation, anorexia, abdominal pain, nausea, vomiting, ileus
- Ileus can lead to megacolon
- Ascites is not common
- These gastric complications may also cause issues with the absorption of oral medications
- Gastrointestinal bleeding can occur as myxedema has a higher risk of bleeds due to coagulopathy-related complications

Hematologic Manifestations

- Can increased risk of bleeding due to an acquired von Willebrand syndrome (reduced synthesis) and a decrease in factors V, VII, VIII, IX, and X
- This is unlike those with only mild hypothyroidism, which causes a hypercoagulable state
- Anemia is common (normocytic or macrocytic)

Hypothermia

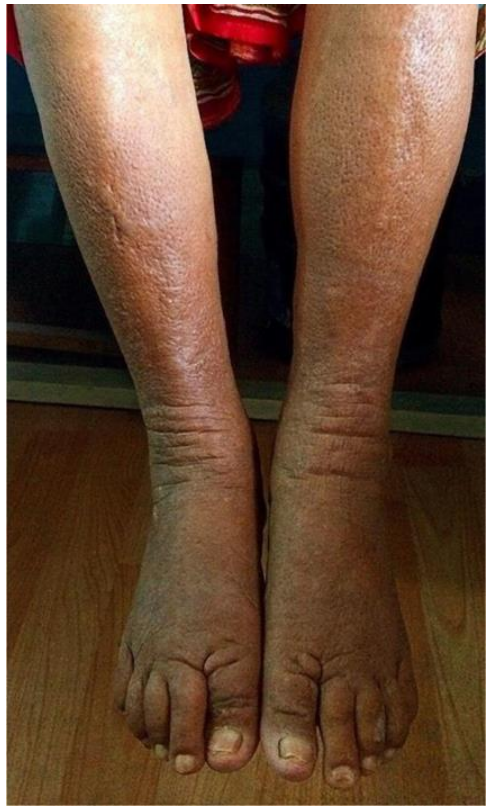
- Hypothermia is defined as a core body temperature less than 35˚C (96 F)
- May present as severe hypothermia
- But not every patient is hypothermic, and some patients may be normothermic
- History of cold intolerance is a clue to the diagnosis

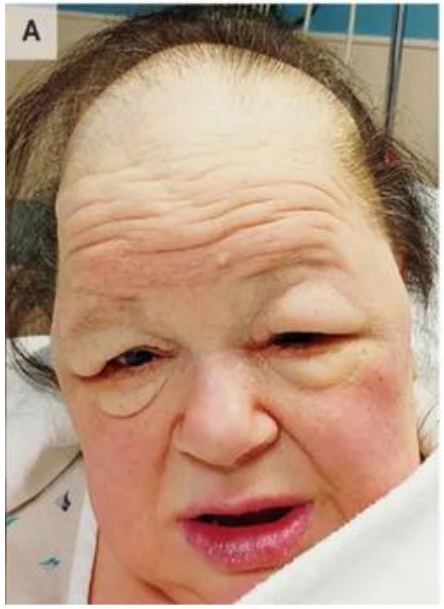
hypoglycemia

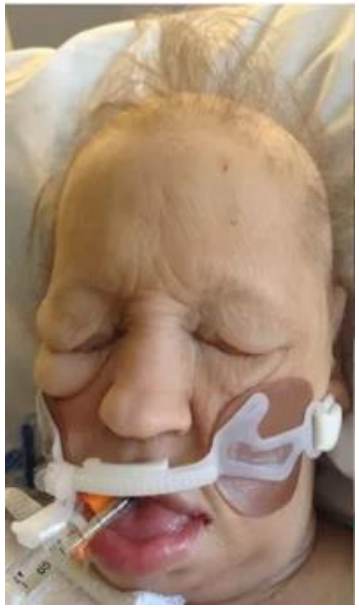
- May require IV dextrose; follow serial glucose levels
- Hypoglycemic should improve somewhat with steroid administration

Skin manifestations

- Dry, cool skin
- Alopecia
- Myxedema (Non-pitting edema of hands/ankles/ face, Hoarseness, macroglossia),
- Loss of hair outer third of the eyebrows (madarosis)







Investigations in “myxedema coma”/decompensated hypothyroidism

- Decompensated hypothyroidism is a clinical diagnosis based on clinical features in the context of hypothyroidism
- The extent of laboratory abnormalities doesn't differentiate compensated vs. decompensated hypothyroidism
- Labs will show hypothyroidism
- A wide range of labs are seen in decompensated hypothyroidism, possibly because this may itself suppress hypothalamic function, thereby reducing the TSH level

Other Laboratory Abnormalities in “myxedema coma”/decompensated hypothyroidism

- Anemia (either normocytic or macrocytic anemia) and leukopenia
- Elevated creatinine phosphokinase can lead to misdiagnosis of myocardial infarction
- Elevated transaminases
- Hyperlipidemia due to inhibition of lipoprotein lipase enzyme
- Hypoglycemia due to downregulation of metabolism
- Hyponatremia with low serum osmolarity and elevated creatinine (increase ADH with a decreased ability of kidneys to excrete water)

Management principles in “myxedema coma”/decompensated hypothyroidism

IV hydrocortisone

- Rationale: Hypothyroidism may be associated with adrenal insufficiency, either due to pituitary disease or as a multifocal autoimmune disorder
  - Giving thyroid hormone *without* steroid can precipitate adrenal crisis
- Hydrocortisone 100 mg IV q8hr is the standard therapy
- Hydrocortisone should be given *prior* to thyroid hormone administration (although this could be less important for levothyroxine, which takes hours to work)
- Patients may be weaned off steroid fairly rapidly, once they are hemodynamically stable and improving

IV levothyroxine (T4) = backbone therapy

- 1st day: Loading dose of 200-400 micrograms IV push
  - Consider using the lower end of the dose range in patients who are elderly, have low body weight, or a history of coronary artery disease or arrhythmia
  - Lower doses should also be used in patients who are being treated with liothyronine
- This dose repletes the peripheral hormone pool
- Safe to give empirically (e.g. if there is a delay in labs returning)
  - T4 is the *inactive* form of thyroid hormone, so this won't cause any immediate effects
  - The normal amount of circulating T4 is ~1000 mcg. So, if the patient doesn't actually have hypothyroidism, giving 200-400 mcg of levothyroxine won't have much effect
- Subsequently, the maintenance dose is 1.2 micrograms/kg IV daily. Or, simply 100 mcg IV daily for most patients.
- Oral thyroid replacement shouldn't be used in decompensated hypothyroidism, because GI absorption may be erratic in this situation

liothyronine (T3) = adjunctive therapy

basics

- T3 is the activated form of thyroid hormone
- Normally the body converts T4 into T3, but this conversion can be impaired in decompensated hypothyroidism. Therefore, T3 could be beneficial in combination with T4 to jump-start recovery
- However, any more aggressive treatment strategy could carry an increased risk of arrhythmia

Indications?

- Liothyronine isn't necessarily mandatory, but it *may* be given as adjunctive therapy in combination with thyroxine. It's probably sensible to reserve liothyronine for more severe situations (e.g. intubated or shocky patients)

Dose?

- The loading dose is 5-20 micrograms IV, followed by a maintenance dose of 2.5-10 micrograms IV q8hr
- Use the lower end of the dose range in smaller or older patients and patients with a history of coronary disease or arrhythmia
- Discontinue once recovering (e.g. improved consciousness) or if T3 levels become elevated
- If you don't have IV liothyronine, oral liothyronine may be used instead. The oral bioavailability is ~95%, although absorption may well be lower in severe, chronic hypothyroidism

Follow up

- **check thyroid hormones every 1-2 days (TSH, free T4, T3)**
- If TSH fails to decrease, the patient may require higher dosing of thyroid hormone.
  - However, TSH typically falls at a rate of ~50% per *week*
- High T3 suggests excess administration of liothyronine
- Avoid drawing labs shortly after administering exogenous T3
- Free T4 should normalize within four days of starting therapy
- Endocrinology should be involved, so discuss the results with them

Supportive care

hypothermia management

- Warm clothing, Bair Hugger, warm fluids (40 to 42 ° C), Inhalation of heated (40 to 45° C) humidified oxygen, lavage (40 to 45° C), Extracorporeal core rewarming (ECR), are options depending on the severity of hypothermia

hypoglycemia

- May require IV dextrose; follow serial glucose levels
- Hypoglycemic should improve somewhat with steroid administration

hyponatremia

- Severe hyponatremia may be a contributory factor towards seizure and delirium. This should be treated according to the guidance
- Mild hyponatremia will resolve with thyroid supplementation

Respiratory support

- Intubation and mechanical ventilation may be required due to coma
- Macroglossia may make intubation more challenging

cardiovascular support

- Tamponade may rarely require drainage. However, these patients tend to bleed and pericardial effusions will improve over time following treatment with thyroid hormone. Therefore, if it's possible to avoid pericardiocentesis, this may be wise
- Patients may be volume depleted, so titrated fluid resuscitation is necessory
- If hypothermia is severe, central temperature should be managed before peripheral rewarming together with adequate fluid resuscitation to avoid shock
- Shock may be pressor-refractory until thyroid hormone is administered

Hematologic support

- For hemorrhage, consider addition of desmopressin (DDAVP 0.3 mcg/kg IV)
- von Willebrand syndrome won't cause alteration in standard coagulation labs, so empiric therapy may be needed
- Acquired von Willebrand syndrome is reversible with T4 therapy

Treatment of the cause

The trigger of decompensated hypothyroidism should be aggressively investigated and treated. This most often may involve…

- **sepsis**
  - Consider empiric therapy for sepsis
  - Decompensated hypothyroidism can mask may features of sepsis (including fever and leukocytosis)

Summary

- Common elderly presentations like falls may not always be straightforward. Need to see the bigger picture
- Rather than thinking about “myxedema coma”: we need to think about compensated vs decompensated hypothyroidism which increases the diagnostic yield
- A high index of suspicion, early recognition, admission to intensive care units, and treatment with intravenous levothyroxine and hydrocortisone are paramount in the management of decompensated hypothyroidism
- Do not forget to look for a precipitating event (e.g. sepsis) in myxedema coma

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