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HOW DO I MANAGE IMMUNOTHERAPY-INDUCED HYPOPHYSITIS?

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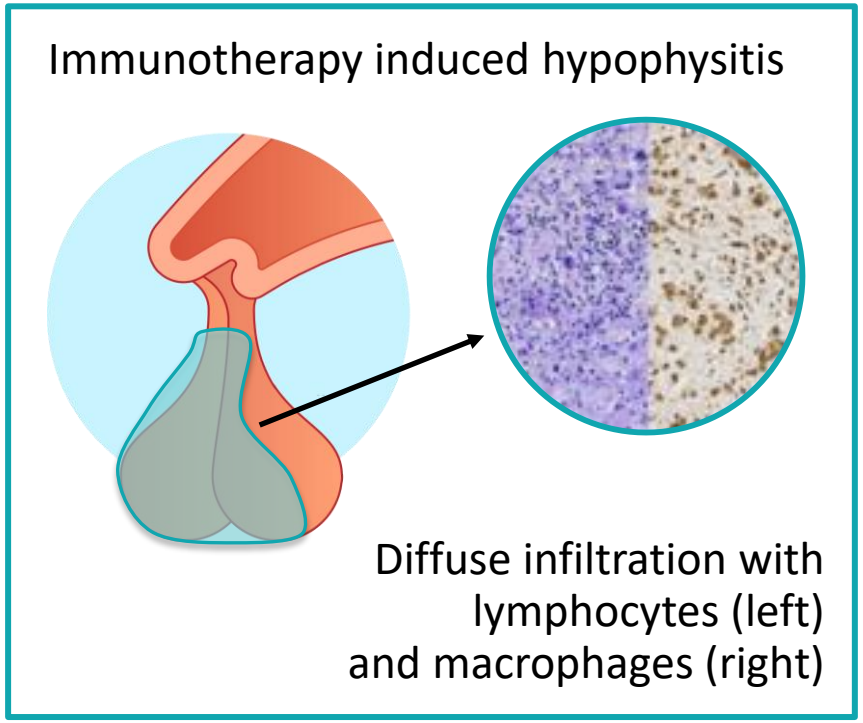
DISCLOSURES

- Dr Langlois has received grants and consultancy fees from Novartis and Pfizer

HOW DO I MANAGE IMMUNOTHERAPY-INDUCED HYPOPHYSITIS

- Establishing diagnosis

- Management
  - Hormonal replacement
  - Low-dose versus high-dose steroids
  - When to hold immunotherapy

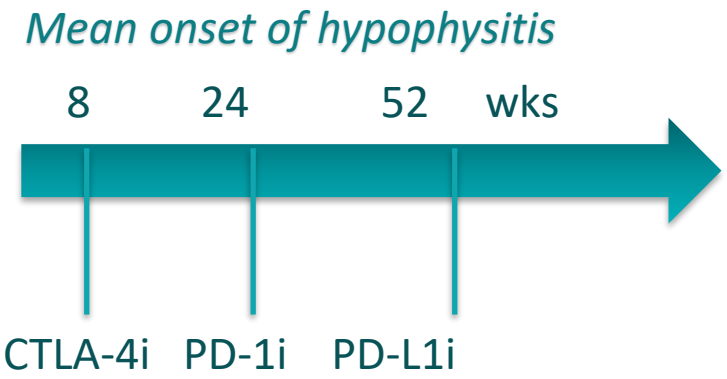


Langlois F, et al. J Clin Endocrinol Metab. 2021. DOI: 10.1210/clinem/dgab672

DIAGNOSIS

DIAGNOSIS

- Presumptive diagnosis based on:
  - Active or recent immunotherapy
    - As early as 4 weeks after initiation, up to 6 months after cessation
    - Median onset at 2-3 months
  - Symptoms
    - Hormonal deficits: fatigue, nausea, orthostatism
    - Headaches
    - Rare visual disturbances: visual field defects, ophtalmoplegia
  - Imaging and laboratory confirmation



- Differential diagnosis with
  - Other causes of hypopituitarism : sellar masses, acute illness, …
  - Primary causes of adrenal insufficiency: post exogenous steroids, very rare 2nd immunotherapy

CTLA-4i, cytotoxic T lymphocyte-associated antigen 4 inhibitor; DI, diabetes insipidus; PD-1i, programmed death 1 inhibitor; PD-L1i, programmed death ligand 1 inhibitor

Fernandes S, et al. Endocrinol Metab Clin North Am. 2020;49(3):387-99

DIAGNOSIS

- Who suspects the diagnosis
  - Oncologist
  - Primary care provider
  - Acute care provider
  - … rarely endocrinologists !

- Based on
  - Regular hormonal work-up with immunotherapy
    - *monthly during the first 6 months*
    - *every 3 months for the next 6 months*
    - *every 6-12 months thereafter (as clinically indicated)*
  - Directed labs ordered for new symptoms

→ Including
- Electrolytes
- TSH, free T4
- Cortisol

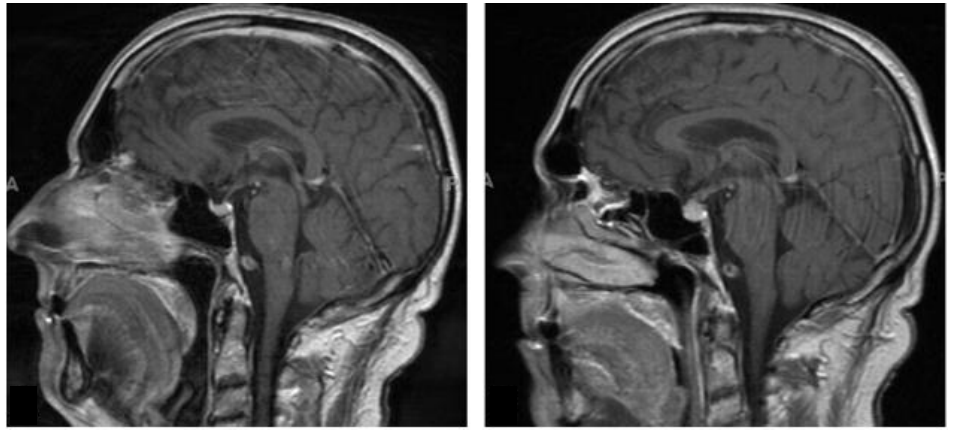
Mortensen MJ, et al. US Endocrinology. 2020;16(2):117-24

DIAGNOSIS

- Laboratory: electrolytes, pituitary function tests
  - Predominant adrenal insufficiency – often isolated with PD-1 and PD-L1 inhibitors
  - May be associated with TSH or LH-FSH deficits (CTLA-4 inhibitors)
  - Very rare DI $\rightarrow$ *think about other diagnosis, such as metastasis or other causes of hypophysitis*
- Imaging: pituitary dedicated MRI
  - Mild gland hypertrophy, stalk thickening, heterogeneous enhancement
    - May precede development of hypopituitarism
  - Can be normal
    - PD-1 and PD-L1 inhibitor >> CTLA-4 inhibitor

⬇

- Visual fields assessment if close to optic chiasm



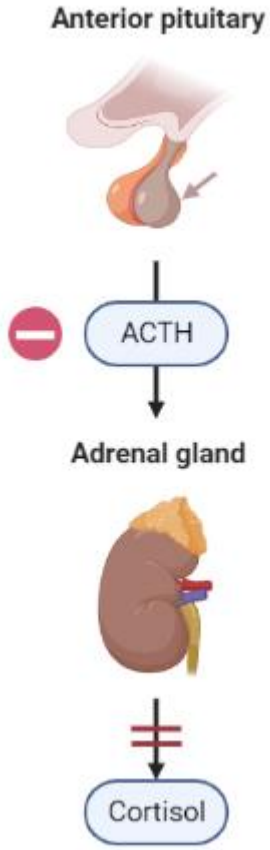
CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DI, diabetes insipidus; FSH, follicle-stimulating hormone; LH, luteinising hormone; MRI, magnetic resonance imaging; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TSH, thyroid-stimulating hormone

Carpenter KJ, et al. AJNR Am J Neuroradiol. 2009;30(9):1751-3

HORMONAL EVALUATION

- Adrenal insufficiency
  - Low cortisol
    - <3-5 µg/dL = diagnosis
    - 3-15 µg/dL = grey zone → ACTH stimulation testing
      may be falsely normal in the setting of acute event (<4-6 weeks)
    - >15 µg/dL = normal
  - Electrolytes
    - Hyponatraemia (common, up to 50% of patients)
    - Normal K+
  - Interpretation: recent exogenous steroids, dysalbuminaemia

    ⬇
  - Measure ACTH levels to confirm central aetiology



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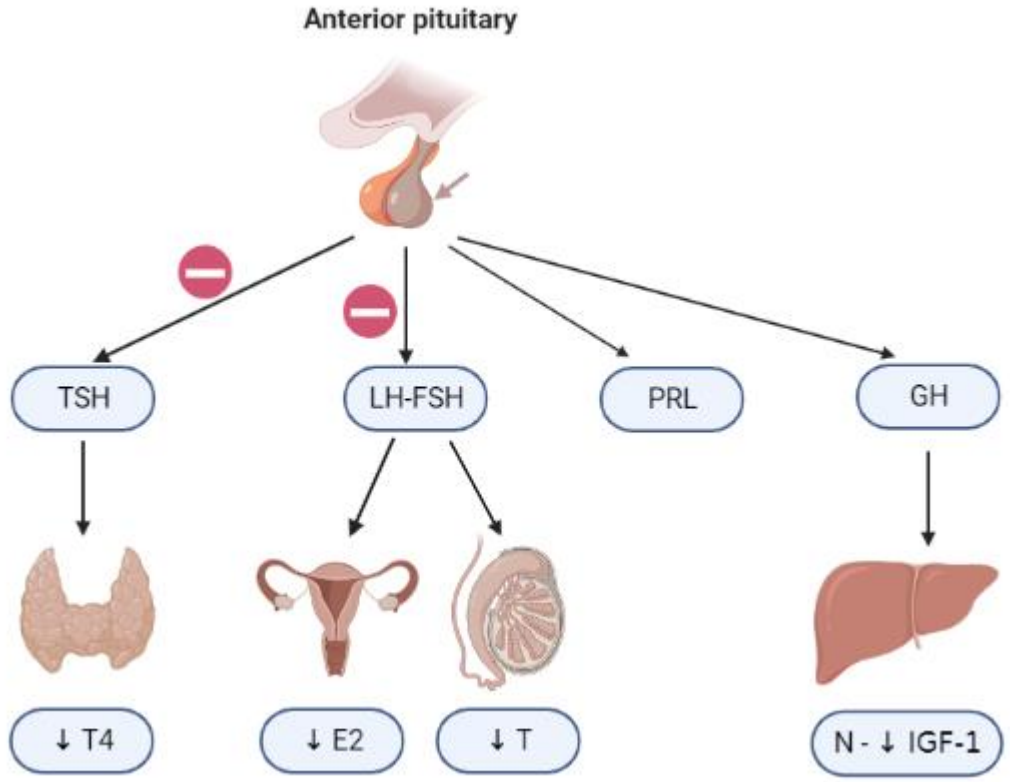
ACTH, adrenocorticotropic hormone; K, potassium

Faje AT et al. J Clin Endocrinol Metab. 2014;99:4078-85

HORMONAL EVALUATION

- Central hypothyroidism
  - Low free T4 and inappropriately low or normal TSH
  - Also possible euthyroid sick syndrome
- Central hypogonadism
  - Hypophysitis versus acute illness
- Prolactin
  - Often normal or low
  - Hyperprolactinaemia is unusual
- IGF-1
  - Optional
  - Low or normal



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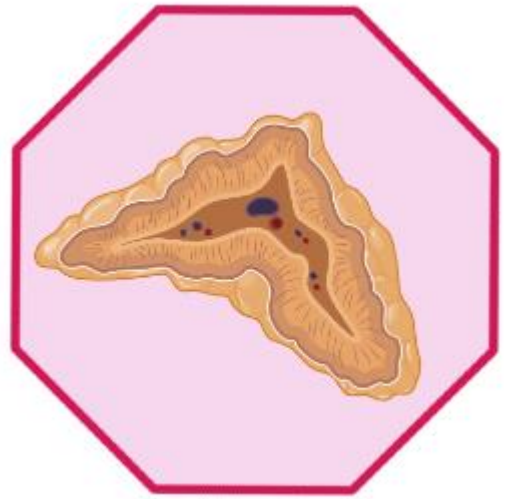
E2, oestradiol; GH, growth hormone; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinising hormone; PRL, prolactin; T, testosterone; T4, thyroxine; TSH, thyroid-stimulating hormone

Chang LS, et al. Endocr Rev. 2019;40(1):17-65; Faje AT, et al. J Clin Endocrinol Metab. 2014;99:4078-85

MANAGEMENT

HORMONAL REPLACEMENT

- Adrenal
  - Prompt replacement
  - Low-dose steroids: physiological replacement
    - Hydrocortisone 10-12 mg/m2 ≈ 15-20 mg per day
    - In most cases
  - Patient education
    - Sick day management and stress dosing
  - Medic-Alert bracelet



  - Moderate dose (prednisone 0,5-1 mg/kg)
    - For moderate symptoms: moderate headaches, no visual disturbances, mild to moderate hypoNa
    - Followed by slow tapering

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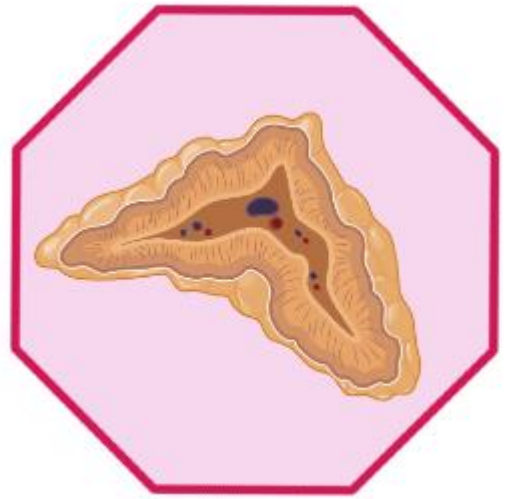
BP, blood pressure; Na, sodium

Brahmer JR, et al. J Clin Oncol. 2018;36(17):1714-68; Haanen JBAG, et al. Ann Oncol. 2017;28(suppl_4):iv119-42; Mortensen MJ, et al. US Endocrinology. 2020;16(2):117-24

HORMONAL REPLACEMENT

- Adrenal (continued)
  - High-dose steroids (methylprednisolone or hydrocortisone 1-2 mg/kg IV per day
    - Indicated in
      - Adrenal crisis
      - Concurrent acute illness
      - Mass effect: severe headaches or visual deficits
      - Severe hyponatraemia
    - Not shown to improve hormonal recovery
    - Does not reduce immunotherapy's effects
  - When improvement: change to prednisone 1 mg/kg per day
  - Wean progressively over 1 month to prednisone 5 mg
  - Followed by physiological hydrocortisone



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IV, intravenous

Brahmer JR, et al. J Clin Oncol. 2018;36(17):1714-68; Haanen JBAG, et al. Ann Oncol. 2017;28(suppl_4):iv119-42

HORMONAL REPLACEMENT

- Thyroid
  - After hydrocortisone replacement is initiated
  - Levothyroxine : start with partial replacement
    - 25-50 µg initial dose in frail patients
    - 0.8-1 µg/kg in otherwise healthy patients
  - Reassess with free T4 after 4 weeks
    - 1.6 µg/kg for full-dose replacement
    - Aim for mid-normal free T4
    - TSH is unreliable, but should be monitored in case of potential recovery
- Testosterone and estrogen replacement
  - Individualise
  - Contra-indicated in hormono-dependent cancers (prostate, breast, uterus)
- GH : contra-indicated if active cancer

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GH, growth hormone; T4, thyroxine; TSH, thyroid-stimulating hormone

Brahmer JR, et al. J Clin Oncol. 2018;36(17):1714-68; Haanen JBAG, et al. Ann Oncol. 2017;28(suppl_4):iv119-42

HOLDING OR CONTINUING IMMUNOTHERAPY?

- Continue immunotherapy for most cases, along with hormonal replacement
  - Discontinuing immunotherapy : not shown to improve outcome

- Hold immunotherapy if moderate to severe hypophysitis, e.g.,:
  - In acute event, awaiting patient stabilisation (e.g., correction of severe hyponatraemia)
  - If mass effect and severe headache
  - If significant hyponatraemia

- Resume immunotherapy
  - When patient is stable, after 4-7 days of hormonal replacement
  - No recurrence of hypophysitis reported upon re-initiation

Angelousi A, et al. Neuroendocrinology. 2020;110(9-10):822-35; Brahmer JR, et al. J Clin Oncol. 2018;36(17):1714-68; Haanen JBAG, et al. Ann Oncol. 2017;28(suppl_4):iv119-42

MONITORING

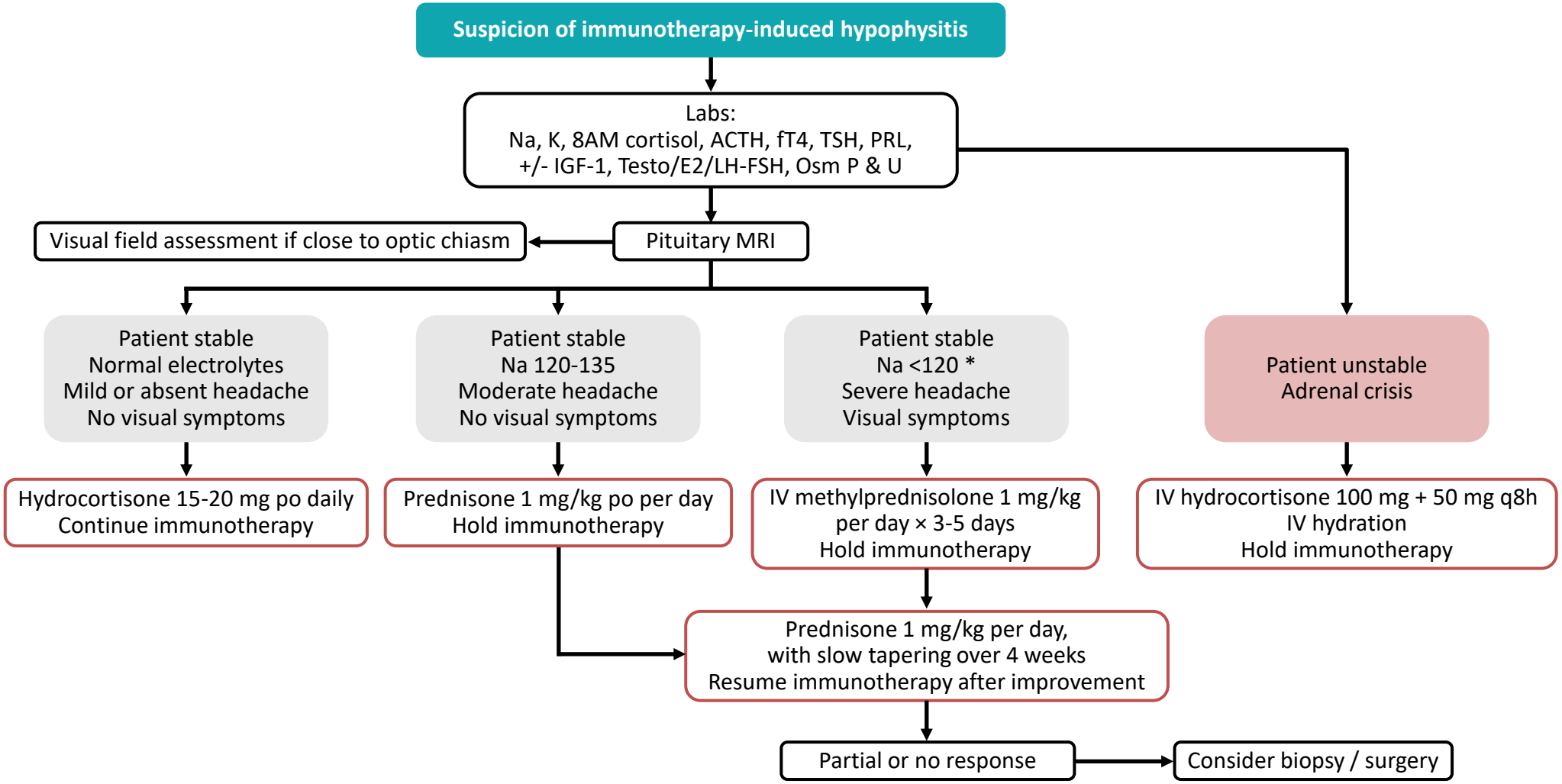
- Potential for recovery of hormonal function
  - Thyroid axis recovery in 6-64%
  - Gonadal axis recovery in 11-57%
  - Adrenal insufficiency almost always persistent
- Reassess hormonal function during follow up

- MRI will normalise in almost all patients
  - Within 1-2 months
  - May leave atrophic pituitary or partially empty sella

MRI, magnetic resonance imaging

Castillero F, et al. Future Oncol. 2019;15(27):3159-69; Haanen JBAG, et al. Ann Oncol. 2017;28(suppl_4):iv119-42

MANAGEMENT ALGORITHM



* In cases of severe hyponatremia, also consider hypertonic saline

ACTH, adrenocorticotropic hormone; E2, oestradiol; FSH, follicle-stimulating hormone; fT4, free thyroxine; IGF-1, insulin-like growth factor 1; IV, intravenous; K, potassium; LH, luteinising hormone; MRI, magnetic resonance imaging; Osmo, osmolality; Na, sodium; P, plasma; po, orally; PRL, prolactin; q8h, every 8 hours; Testo, testosterone; TSH, thyroid-stimulating hormone; U, urine

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