HYPONATREMIA HAZE: IPILIMUMAB, NIVOLUMAB AND STEROID TAPERS

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INTRODUCTION:

Hyponatremia is common in hospitalized patients. Symptoms can be mild including headache, malaise, weakness, nausea, vomiting and confusion, or severe including coma, seizure, brainstem herniation and death. There are multiple causes of hyponatremia including glucocorticoid deficiency, stress, syndrome of inappropriate antidiuretic hormone (SIADH), hypothyroidism, liver, cardiac and renal disease, intracranial disease processes and drug induced[1,2] including new immunotherapeutic agents. Ipilimumab, a Cytotoxic T-Cell Antigen 4 (CTLA-4) inhibitor and Nivolumab, an anti-programmed cell death-1 receptor monoclonal antibody, are used to treat metastatic melanoma and have shown evidence of immune mediated side-effects including hypophysitis with use of Ipilimumab and Nivolumab [3,4,5,7] and primary adrenal insufficiency with Nivolumab [6].

CASE PRESENTATION:

An elderly man with metastatic melanoma, treated with Ipilimumab and Nivolumab, refractory HTN, severe PTSD and uncontrolled diabetes mellitus presents with subacute weakness, fatigue, confusion and nausea. Treatment with Ipilimumab was complicated by drug induced pneumonitis, with recent steroid burst and taper ending 1 week prior to presentation.

PHYSICAL EXAM:
- Afebrile, non-tachycardic
- normotensive *but* orthostatic
- Neuro: Non-focal exam, alert, oriented
- Chest/CV: CTAB, RRR, no MGR

LABS:
- Sodium 122
- Serum Osmolality 266
- Urine osmolality 475
- Urine Sodium 43
- Serum Cortisol 0.5 (low)
- ACTH 4.0 (low)
- TSH, Free T4 and Prolactin all normal
- Normal CBC and LFTs

IMAGING:
- MRI Brain with/without contrast: no clear evidence of hypophysitis, limited by motion artifact.

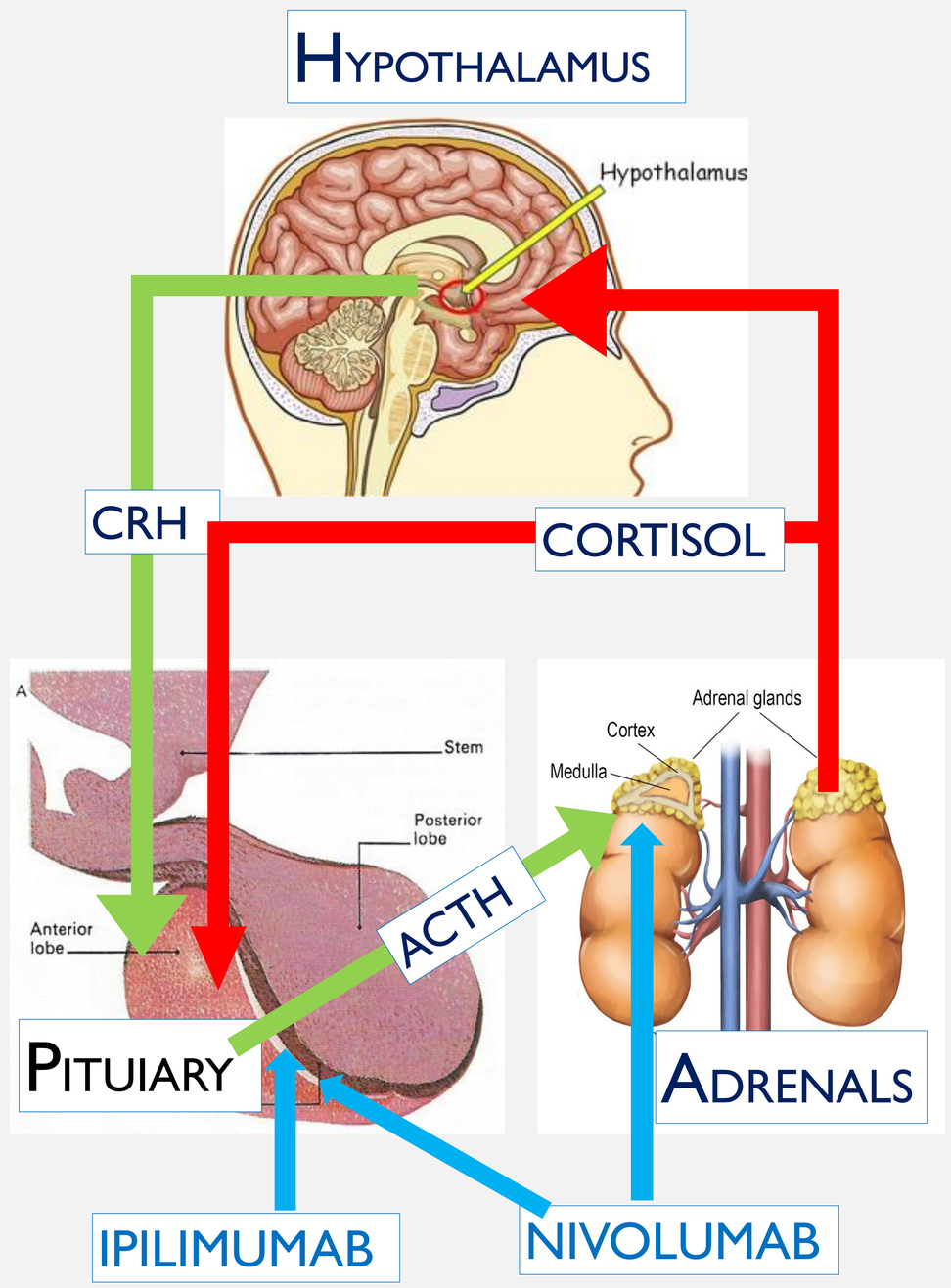

IMAGE REFERENCES
http://brainmadesimple.com/uploads/7/8/8/5/7885523/_1397040.jpg
http://www.daviddarling.info/images3/pituitary_lobes.jpg
https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022159/?figure=1

DISCUSSION:

This patient had secondary adrenal insufficiency manifested by weakness, fatigue, confusion, orthostatic hypotension, relative hypotension and hypoglycemia (blood glucose 125, baseline 220-250). Knowledge of his previous drug exposures made diagnosis and initiation of treatment with steroids possible quickly.

His adrenal insufficiency was due either to hypophysitis due to Ipilimumab or Nivolumab, or exogenous steroid exposure. Unfortunately, diagnosis could not be determined during his hospital stay. The diagnosis was difficult as intracranial imaging could not be obtained until 3-4 days after initiation of high dose steroid therapy and was severely degraded by motion artifact limiting ability to evaluate for hypophysitis.

Unfortunately, the hormone insufficiency induced by hypophysitis is not always reversible while exogenous steroid induced adrenal insufficiency typically is. This patient will undergo slow steroid taper with cosyntropin stimulation test prior to removal of therapy to see if steroid therapy can be withdrawn or whether he is destined to life-long steroid therapy.

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TAKE HOME POINTS:

- When faced with "normal" data, keep your patient in mind.
- Increasing use of new immunotherapies requires provider awareness of the action of these agents and their complications.
- When patients are on immunotherapies there should be a high index of suspicion and low threshold for testing.