Care Step Pathway – Hypophysitis (inflammation of the pituitary gland)

Assessment

Look:
- Does the patient appear fatigued?
- Does the patient look listless?
- Does the patient look ill?
- Does the patient look uncomfortable?
- Is the patient an older male, receiving anti-CTLA-4 with or without anti-PD-1/PD-L1?

Listen:
- Does the patient report:
  - o Fatigue?
  - o Headache?
  - o Loss of appetite?
  - o Change in energy?
  - o Dizziness?
  - o Nausea/vomiting?
  - o Altered mental status?
  - o Visual disturbances?
  - o Fever?
  - o Changes in libido?

Recognize:
- Low levels of hormones produced by pituitary gland (ACTH), TSH, FSH, LH, GH, prolactin)
- Brain MRI with pituitary cuts: enhancement and swelling of the pituitary gland
- S/sx ACTH deficiency: fever, hypotension, electrolyte disturbances (hyponatremia), altered consciousness
- DDX primary adrenal insufficiency: low AM cortisol and high AM ACTH
- DDX primary hypothyroidism: low free T4 and high
- Predominance in older males, those receiving ipilimumab
- Mild hyponatremia

Grading Toxicity (Overall)

Grade 1 (Mild)
Asymptomatic or mild symptoms; clinical or diagnostic observation only (headache, fatigue)

Grade 2 (Moderate)
Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs

Grade 3 (Severe)
Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or existing hospitalization indicated; limiting self-care ADLs

Grade 4 (Potentially Life-Threatening)
Urgent intervention required (severe ataxia)

Grade 5 (Death)

Management

Overall Strategy (treatment is directed at replacement of deficient hormone/s):
- Endocrinology consult
- Diagnostic workup for any patient where pituitary dysfunction is suspected based on symptoms or routine lab monitoring, morning. Obtain ACTH and morning cortisol (best before 9 am), TSH *and* fT4, electrolytes
- Consider obtaining LH & testosterone in males and FSH & estrogen in premenopausal females with fatigue, loss of libido, and mood changes, or oligomenorrhea (females)
- Consider MRI brain w/wo contrast with pituitary or sellar cuts in all patients with new hormonal deficiencies and particularly those with multiple endocrine abnormalities, new severe headaches, or complaints of vision changes and perform for all patients presenting with diabetes insipidus

Grade 1 (Mild)
Continue ICI; begin hormone replacement for corresponding hormone deficiency

Grade 2 (Moderate)
Consider holding ICI until patient is stabilized on replacement hormone. Consider oral pulse dose therapy in patients with MRI findings of swelling or threatened optic chiasm compression (prednisone 1 mg/kg/d (or equivalent). Taper over 1-2 weeks and transition to physiologic maintenance therapy once down to 5 mg

Grade 3 (Severe) and 4 (Potentially Life-Threatening)
Hold ICI until patient is stabilized on replacement hormone/s. Assess need for urgent intervention (hospitalize or ED evaluation) for IV hydration or monitored free water replacement if DI; IV stress dose steroids of hydrocortisone 50-100 mg Q6-8 hours initial dosing then transition to prednisone 1-2 mg/kg daily (or equivalent) tapered over at least 1-2 weeks to physiologic maintenance in patients with significant swelling on MRI, optic chiasm compression, severe headache, or visual changes. Taper stress dose corticosteroids down to oral maintenance doses over 5-7 days

When multiple hormones are low, priority should be directed to treating the cortisol deficiency first, as other hormones accelerate the clearance of cortisol and can precipitate adrenal crisis.

See Implementation for specifics on endocrinology consultation, education, and emergency precautions.

Implementation:
- Ensure that MRI is ordered with pituitary cuts or via pituitary protocol
- Anticipate temporary treatment hold of ICI until patient is stable on hormone replacement
- It is essential patients receive appropriate education and counseling about: stress dosing for sick days, use of emergency injectables, when to seek medical attention for impending adrenal crisis, need for medical alert bracelet or necklace. Recommend early endocrinology consultation
- Endocrine consultation must be part of planning before surgery or high stress treatments such as cytotoxic chemotherapy

*Administering Corticosteroids:
Routine use of high-dose glucocorticoid is not recommended and should only be used for patients with mass effect or severe headache

RED FLAGS:
- **Symptoms of adrenal insufficiency**
- **New onset of severe headache or vision changes**

ACTH = adrenocorticotropic hormone; ADLs = activities of daily living; DDX = differential diagnosis; FSH = follicle-stimulating hormone; GH = growth hormone; ICI = immune checkpoint inhibitor; LH = luteinizing hormone; MRI = magnetic resonance imaging; po = by mouth; TSH = thyroid stimulating hormone.