

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?

Listen:

- Does the patient report:
 - o Change in energy?
 - o Headache?
 - 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
- Hypotension
- Electrolyte disturbances
- DDX adrenal insufficiency: low cortisol and high ACTH
- DDX primary hypothyroidism: low free T4 and high TSH

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 of existing hospitalization indicated; limiting self-care ADLs

Grade 4 (Potentially Life-Threatening)

Urgent intervention required (severe ataxia)

Grade 5 (Death)

Management

Overall Strategy:

- Consider endocrinology consult
- Diagnostic workup should be initiated if not already done: Monitor levels of ACTH, AM cortisol, TSH, T4, and electrolytes
- Additional workup for low libido, mood changes, and fatigue may include LH, FSH, testosterone, and estradiol
- Analgesia as needed for headache (discuss with neurologist if resistant to paracetamol and NSAIDs)
- Ipilimumab to be withheld for any symptomatic hypophysitis and discontinued for symptomatic reactions persisting ≥ 6 weeks or for inability to reduce steroid dosage to ≤ 7.5 mg prednisone or equivalent per day
- Nivolumab to be withheld for Grade 2/3 hypophysitis and permanently discontinued for Grade 4 hypophysitis. Pembrolizumab to be withheld for Grade 2 hypophysitis and withheld or discontinued for Grade 3/4 hypophysitis
- 1 mg/kg methylprednisolone (or equivalent) IV to be given daily*
 - o If given during acute phase, may reverse inflammatory process
- To be followed with prednisone 1-2 mg/kg daily with gradual tapering over at least 4 weeks
- May hold checkpoint inhibitors for any symptoms suspect for hypophysitis and restart after stabilized on hormone therapy
- Long-term supplementation of affected hormones is often required
 - o Secondary hypothyroidism requiring levothyroxine replacement
 - o Secondary hypoadrenalism requiring hydrocortisone replacement
 - Typical dosage: 20 mg qAM and 10 mg qPM
 - o Steroids should start several days prior to any thyroid replacement to prevent adrenal crisis
- Assess risk of opportunistic infection based on duration of steroid taper (and consider prophylaxis if needed)
- Collaborative management approach with endocrinology (particularly if permanent loss of organ function)
- Medical alert bracelet is indicated

Implementation:

- ACTH and thyroid panel should be checked at baseline and prior to each dose of ipilimumab
- Ensure that MRI is ordered with pituitary cuts or via pituitary protocol
- Anticipate treatment with corticosteroid and immunotherapy hold
- Review proper administration of steroid
 - o Take with food
 - o Take in AM
- Educate patient regarding possibility of permanent loss of organ function (pituitary; possibly others if involved [thyroid, adrenal glands])
- Advise patients about medical alert bracelet, etc., stress doses of hydrocortisone or infection, etc.

*Administering Corticosteroids:

Steroid taper instructions/calendar as a guide but not an absolute

- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need & symptomatology
- Steroids cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on steroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review steroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down & report them (taper may need to be adjusted)

Long-term high-dose steroids:

- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron[®]] 1500 mg po daily)
- Consider additional antiviral and antifungal coverage
- Avoid alcohol/acetaminophen or other hepatotoxins
- If extended steroid use, risk for osteoporosis; initiate calcium and vitamin D supplements

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; LH = luteinizing hormone; MRI = magnetic resonance imaging; po = by mouth; TSH = thyroid stimulating hormone.