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

**Assessment**

<table>
<thead>
<tr>
<th>Look:</th>
<th>Listen:</th>
<th>Recognise:</th>
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<tbody>
<tr>
<td>- Does the patient appear fatigued?</td>
<td>- Does the patient report:</td>
<td>- Low levels of hormones produced by pituitary gland (ACTH, TSH, FSH, LH, GH, prolactin)</td>
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<td>- Does the patient look listless?</td>
<td>o Change in energy?</td>
<td>- Brain MRI with pituitary cuts: enhancement and swelling of the pituitary gland</td>
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<tr>
<td>- Does the patient look ill?</td>
<td>o Headache?</td>
<td>- Hypotension</td>
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<td>- Does the patient look uncomfortable?</td>
<td>o Dizziness?</td>
<td>- DDX adrenal Insufficiency: low cortisol and high ACTH</td>
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<tr>
<td></td>
<td>o Nausea/vomiting?</td>
<td>- DDX primary hypothyroidism: low free T4 and high TSH</td>
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<td>o Altered mental status?</td>
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<td>o Visual disturbances?</td>
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<td></td>
<td>o Fever?</td>
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<td></td>
<td>o Changes in libido?</td>
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</table>

**Grading Toxicity (Overall)**

<table>
<thead>
<tr>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
<th>Grade 5 (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or mild symptoms; clinical or diagnostic observation only (headache, fatigue)</td>
<td>Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or existing hospitalization indicated; limiting self-care ADLs</td>
<td>Urgent intervention required (severe ataxia)</td>
<td>*Death*</td>
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</tbody>
</table>

**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 oestradiol
- 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 IV 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:**

* 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.

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