ERABI EVIDENCE-BASED REVIEW of moderate to severe ACQUIRED BRAIN INJURY

# Clinical Guidebook

# 10. Neuroendocrine Function and Disorders after Acquired Brain Injury

**E. Ali Bateman MD, Amber Harnett MSc, Shannon Janzen MSc, Robert Teasell MD FRCPC**

Ontario Neurotrauma Foundation
Fondation ontarienne de neurotraumatologie
LAWSON HEALTH RESEARCH INSTITUTE
Western
St. JOSEPH's HEALTH CARE LONDON

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# Neuroendocrine Function and Disorders after ABI

**By the end of this chapter you should know:**

- The most common neuroendocrine disorders following an acquired brain injury (ABI)
- How to identify neuroendocrine disorders in individuals with an ABI
- How and when to screen for/test neuroendocrine disorders in individuals with an ABI
- Potential case management scenarios

## 10.1 Introduction to Neuroendocrine Disorders Post ABI

Neuroendocrine dysfunction is a common and potentially serious complication of acquired brain injury (ABI) that is increasingly recognized as a cause of morbidity in this population. Neuroendocrine disorders result from disruption of or injury along the hypothalamic-pituitary axis, an area of the brain that regulates physiological functions (Sandel et al., 2007). This guidebook chapter describes neuroendocrine disorders arising from disruption of hypothalamic-pituitary axis function and their management.

### 10.1.1 Anatomy and Physiology of the Pituitary Gland

The pituitary gland is a pea-sized neuroendocrine gland that sits beneath the optic chiasm in the sella turcica in the centre of the skull. The pituitary gland connects to the hypothalamus via the pituitary stalk or infundibulum.

The pituitary gland consists of two lobes: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The anterior lobe contains glandular cells that secrete hormones into the circulation via the portal capillary network, a system of blood vessels that link the pituitary gland with the systemic circulation. The anterior pituitary is controlled by the hypothalamus via a vascular portal system inside the pituitary stalk, which provides the blood supply for the anterior lobe. The vessels within the pituitary stalk are vulnerable to injury in ABI, which can lead to ischemia of the anterior lobe. The posterior lobe is made of axons and nerve terminals of nerves located in the hypothalamus. These nerve projections travel in the pituitary stalk to the posterior lobe, and then release hormones directly into the portal capillary network to enter the systemic circulation. The posterior lobe is vulnerable to direct trauma that injures the axons, particularly at the level of the pituitary stalk, but is less vulnerable to ischemic injury than the anterior lobe. Long-term recovery of posterior pituitary lobe function is also favourable, as the axons can regrow from the hypothalamus over time.

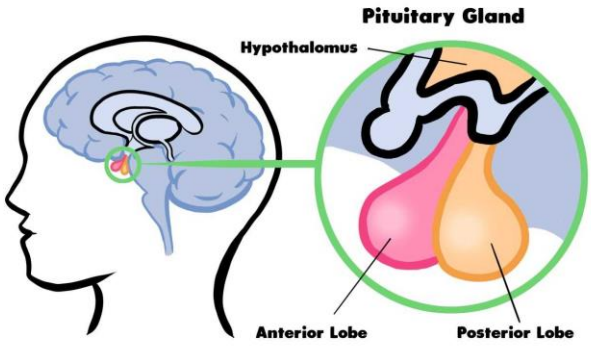


**Figure 10.1: Anatomy of the pituitary gland.**

Together with the hypothalamus, the pituitary gland regulates endocrine function and serves a crucial role in homeostasis. The hypothalamus directs the anterior lobe's hormone production by secreting

releasing or inhibiting hormones that travel to the pituitary via a vascular portal system within the pituitary stalk. The hypothalamus directly controls the hormones released from the posterior lobe, as the axons and nerve terminals that make up the posterior lobe are direct projections from the hypothalamus. The hypothalamus determines which hormones should or should not be secreted from the anterior and posterior lobes using complex feedback loops from the systemic circulation. These feedback loops are crucial to prevent over- or under-production of neuroendocrine hormones and maintain homeostasis.

## 10.1.2 Pituitary Hormones and Bodily Responses

The anterior lobe of the pituitary gland produces six hormones: Prolactin (PRL), Adrenocorticotrophic hormone (ACTH), Growth Hormone (GH), Thyrotropin Stimulating Hormone (TSH), Follicle Stimulating Hormone (FSH), and Luteinizing Hormone (LH). The posterior lobe of the pituitary gland produces two hormones: Antidiuretic Hormone (ADH, sometimes also referred to as vasopressin), and oxytocin. These hormones and the organs they act on are summarized in Table 10.1.

**Table 10.1 Pituitary Hormones and Bodily Responses**

| | Hormone | Hypothalamic Control/Feedback | End Organ Affected and Body Response | Testing |
|---|---|---|---|---|
| Anterior Lobe | PRL | PRL releasing factor and thyrotropin releasing hormone → release of PRL<br>Dopamine → inhibits release of PRL | Mammary gland → lactation | PRL level |
| | ACTH | Corticotropin releasing hormone → release of ACTH | Adrenal gland → glucocorticoid production | Cortisol level (test in a.m.)<br>Serum glucose |
| | GH | Growth hormone releasing hormone → release of GH<br>Somatostatin → inhibits release of GH | Liver produces IGF-1<br>IGF-1 acts on muscle, bone, and other tissues for growth and metabolism | IGF-1 level |
| | TSH | Thyrotropin releasing hormone → release of TSH<br>Somatostatin → inhibits TSH release | Thyroid gland → thyroid hormones for growth and metabolism | TSH level<br>Thyroid hormone (free T4) |
| | FSH | Gonadotropin releasing hormone → release of FSH and LH<br>Luteinizing hormone releasing hormone → release of LH | Ovaries → sex hormone production, menstrual cycles<br>Testes → testosterone production, sperm production | FSH level<br>LH level<br>Testosterone level (men; test in a.m.)<br>Estrogen level (women) |
| | LH | | | |
| Posterior Lobe | ADH | N/A | Kidney → concentrates urine by increasing water resorption | ADH level<br>Serum sodium<br>Urine sodium |
| | Oxytocin | N/A | Uterus → labour contractions<br>Mammary gland → lactation | Oxytocin level |

Note: ADH=Antidiuretic hormone, ACTH= Adreno-corticotropin Releasing Hormone, FSH=Follicle Stimulating Hormone, GH=Growth Hormone, LH=Luteinizing Hormone, PRL=prolactin, TSH=Thyrotropin Stimulating Hormone

## 10.1.3 Epidemiology of Neuroendocrine Dysfunction after ABI

**Q1. What is the prevalence of neuroendocrine dysfunction after an ABI? Which hormones are most commonly affected?**

1. The prevalence of neuroendocrine dysfunction varies widely in different studies; estimates range from 20-70%. The prevalence may be highest in the acute period after injury. Long-term, the prevalence is likely closer to 30%.
2. Growth hormone deficiency, elevated PRL, ADH deficiency (diabetes insipidus), ACTH deficiency, and hypogonadism are the most common abnormalities.

Hypopituitarism, or diminished production of pituitary hormones, is increasingly recognized as a common and potentially serious sequela of ABI. Although neuroendocrine dysfunction was previously thought to be a rare occurrence following an ABI, improved understanding of the incidence suggests that 8-80% of patients may experience hypopituitarism (Makulski et al., 2008; Sirois, 2009). Some studies have suggested that hypopituitarism may be most common in the acute phase of injury, and that the prevalence may decline in the chronic phase of injury; two reviews of the literature found the pooled prevalence of hypopituitarism in the chronic phase of injury was 27-32% (Lauzier et al., 2014; Schneider et al., 2007b).

Although increasingly recognized, the prevalence of specific hormone deficiencies has not been well-established in patients who sustain an ABI. This is due, in part, to variations in prevalence in the acute, subacute, and chronic phases of recovery. The most common presentation of hypopituitarism following an ABI is a single-axis hormone deficiency, which is estimated to occur in 30-40% of patients who sustain an ABI compared to multi-hormone deficiencies, which are estimated to affect 10-15% of patients (Aimaretti et al., 2004a; Benvenga et al., 2000; Kelly et al., 2000; Lieberman et al., 2001). Of the single-axis hormone deficiencies, elevated PRL (30%), GH hormone deficiency (30%), ADH deficiency (diabetes insipidus, DI; 15-50%), adrenocorticotropin-releasing hormone (9-80%), hypogonadism (10-30%), and hypothyroidism (10-30%) are the most well-described (Bondanelli et al., 2004; Hadjizacharia et al., 2008; Hannon et al., 2013; Olivecrona et al., 2013). In some studies, GH is favoured to be the most common single axis deficiency (Bondanelli et al., 2004; Ghigo et al., 2005).

The likelihood of experiencing neuroendocrine dysfunction varies based on a number of factors, including the time since injury. In the acute period following an ABI, neuroendocrine dysfunction or hormonal dysregulation may occur due to immediate responses to injury and critical illness rather than due to injury to the components of the hypothalamic-pituitary axis, and therefore may not result in long-term neuroendocrine disruption (Klose et al., 2007). In the acute phase, monitoring for signs of potentially life-threatening ACTH and ADH deficiency is important, even if these deficiencies may not persist (Hadjizacharia et al., 2008; Hannon et al., 2013; Kelly et al., 2000; Olivecrona et al., 2013; Sesmilo et al., 2007).

## 10.1.4 Risk Factors for Developing Neuroendocrine Dysfunction after ABI

**Q2. What are the risk factors for hypothalamic-pituitary axis dysfunction after an ABI? (Schneider et al., 2007b)**

1. Injury Severity
2. Glasgow Coma Scale score 3-12
3. Location of injury (basal skull fractures, diffuse axonal injury)
4. Increased intracranial pressure
5. Length of intensive care unit stay
6. Length of time post injury

Given the prevalence of neuroendocrine dysfunction following ABI and the variability in the timing of presentation and diagnosis, risk factors for the development of neuroendocrine dysfunction have not been well-established.

**Severity of Injury**

Individuals with moderate or severe ABI are more likely to experience neuroendocrine dysfunction than individuals who sustain mild injuries (INESSS-ONF 2015; Klose et al., 2007; Popovic et al., 2005).

**Table 10.2 Defining Severity of Traumatic Brain Injury (adapted from Veterans Affairs Taskforce 2008 and Campbell 2000)**

| | Mild | Moderate | Severe | Very Severe |
|---|---|---|---|---|
| **Initial Glasgow Coma Scale score** | 13-15 | 9-12 | 3-8 | Not defined |
| **Duration Loss of Consciousness** | <15 minutes* | <6 hours | 6-48 hours | >48 hours |
| **Duration Post-Traumatic Amnesia** | <1 hour* | 1-24 hours | 1-7 days | >7 days |

*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).

Studies evaluating whether individuals who sustain severe ABI are at greater risk of developing neuroendocrine dysfunction than individuals who sustain moderate ABI have yielded mixed results. On the balance of evidence, the risk of developing neuroendocrine dysfunction is likely higher in persons who sustain greater severity ABI (Bondanelli et al., 2004; Cernak et al., 1999; Kleindienst et al., 2009; Klose et al., 2007; Lauzier et al., 2014; Nemes et al., 2015; Prasanna et al., 2015; Schneider et al., 2007a; Tanriverdi et al., 2013). However, this not a consistent finding (Agha et al., 2004; Tanriverdi et al., 2007) possibly because of methodologic differences, timing of assessment (i.e. acute vs. chronic phase of injury), and patient selection.

There is inconsistent evidence as to whether lower Glasgow Coma Scale score correlates with the likelihood of developing neuroendocrine dysfunction: several studies reported Glasgow Coma Scale score was inversely correlated with the likelihood of developing neuroendocrine dysfunction (Agha & Thompson, 2005; Klose et al., 2007; Schneider et al., 2006; Sirois, 2009) whereas other studies did not (Bondanelli et al., 2007; Ghigo et al., 2005).

Limited available evidence suggests that patients with persistent or prolonged disorders of consciousness following ABI are at increased risk of hypothalamic-pituitary axis dysfunction (Estes & Urban, 2005; Klose et al., 2007; Sesmilo et al., 2007). Similarly, limited evidence suggests prolonged admission to the intensive care unit (ICU) has been associated with increased risk of hypopituitarism (Klose et al., 2007; Schneider et al., 2007a). Although disorders of consciousness and prolonged ICU stay may not reflect exclusively a patient's brain injury severity, these factors suggest patients with more severe clinical presentations may be at increased risk of neuroendocrine dysfunction.

**Basal Skull Fractures**

Like severity of injury, basal skull fractures have not been shown to consistently predict increased risk of neuroendocrine dysfunction following ABI. Several studies have demonstrated that basal skull fractures are associated with the development of ADH deficiency (DI) after ABI (Born et al., 1985; Schneider et al., 2007a; Schneider et al., 2008). Moreover, on the balance of evidence, basal skull fractures likely indicate an increased risk for anterior lobe dysfunction as well (Lauzier et al., 2014; Schneider et al., 2008); although, this finding has not been replicated by all studies (Bondanelli et al., 2007).

**Age**

In a systematic review, Lauzier et al. (2014) found that older age was predictive of anterior lobe neuroendocrine dysfunction. All included studies had a mean age <50 years old, reflecting the young age of most patients with ABI (Benvenga et al., 2000). Other studies have yielded similar results (Agha et al., 2004; Bondanelli et al., 2004; Schneider et al., 2006).

**Type of Injury**

Neuroendocrine dysfunction may present following any type of ABI (Klionsky et al., 2016). Several studies have evaluated whether specific types of traumatic brain injury (TBI) may increase a person's risk of neuroendocrine dysfunction with mixed results. Several studies have found no relationship between the type of injury and hypothalamic-pituitary axis dysfunction (Ghigo et al., 2005; Lauzier et al., 2014). Other studies have demonstrated that diffuse axonal injury (Estes & Urban, 2005; Hadjizacharia et al., 2008; Schneider et al., 2008) and penetrating injury may increase risk (Hadjizacharia et al., 2008). Cerebral edema is correlated with increased risk of DI from ADH insufficiency (Behan et al., 2008). Subarachnoid hemorrhage is correlated with increased risk of Syndrome of Inappropriate ADH (SIADH), or excess ADH production (Behan et al., 2008), as well as anterior lobe hormone deficiencies (Khajeh et al., 2015).

## 10.1.5 Pathophysiology and Mechanism of Injury

ABI can affect any component of the hypothalamic-pituitary axis directly (e.g., trauma or injury to the intracranial axis components), or indirectly (e.g., systemic illness or medication(s) that affect the body's normal feedback loops). Multiple intracranial injury mechanisms have been identified as potential disruptors of this system, as outlined in Table 10.3. Injury along the hypothalamus-pituitary axis most commonly occurs at the level of the pituitary stalk or within the pituitary gland (Table 10.4). Although injury to these structures may explain some of the pathophysiology contributing to hormonal dysfunction after ABI, neuroimaging abnormalities are not necessarily predictive of the presence of or type of neuroendocrine disorders. In one study, 7% of individuals with an ABI and concurrent pituitary-hypothalamic dysfunction did not have neuroimaging abnormalities (Benvenga et al., 2000).

The pituitary stalk joins the hypothalamus at the base of the brain with the pituitary gland, which sits within the bony confines of the sella turcica. Due to its anatomical position, the pituitary stalk is particularly vulnerable to shear forces generated in acceleration-deceleration injuries or direct trauma from basal skull fractures. Both the hypothalamus and the posterior lobe are vulnerable to hemorrhage due to their anatomical locations. Ischemic injuries of the anterior pituitary are more common than ischemic injuries to the posterior pituitary. The anterior lobe is susceptible to injury due to its tenuous blood supply via the portal venous system travelling in the pituitary stalk. The vessels in the pituitary stalk provide the anterior pituitary lobe with 90% of its blood supply; this can be disrupted by shear forces, basal skull fracture, and systemic hypoperfusion such as in hypotensive shock (Behan et al., 2008). In the setting of significant cerebral edema, some individuals may develop DI, which results from a failure of the posterior pituitary to secrete ADH. Often, this posterior pituitary dysfunction is transient, and normal ADH production resumes with time and with the resolution of edema (Behan et al., 2008).

**Table 10.3 Intracranial Causes of Hypothalamic-Pituitary Axis Disruption (adapted from Sirois 2009)**

| Type of Intracranial Injury | Mechanism of Injury | Possible Sites and Features of Injury |
|---|---|---|
| Direct | Acceleration-deceleration | Traumatic lesion of pituitary stalk<br>Anterior lobe ischemia/necrosis<br>Posterior lobe hemorrhage |
| | Basal skull fracture | Traumatic lesion of pituitary stalk<br>Direct injury to anterior and/or posterior lobe<br>Direct injury to hypothalamus |
| Indirect | Brain edema | May affect hypothalamus, anterior, or posterior lobe |
| | Hypoxia | May affect hypothalamus, anterior, or posterior lobe |
| | Raised intracranial pressure or hydrocephalus | May affect hypothalamus, anterior, or posterior lobe |
| | Reduced cerebral perfusion from systemic shock | Hypothalamic hypoxic injury<br>Anterior and/or posterior lobe ischemia |
| | Inflammation | May affect hypothalamus, anterior, or posterior lobe |

**Table 10.4 Incidence of Locations of Injuries to the Hypothalamic-Pituitary Axis (Benvenga et al., 2000)**

| Location and Type of Injury | Incidence |
|---|---|
| Hemorrhage of the hypothalamus | 29% |
| Hemorrhage of the posterior lobe | 26% |
| Infarct of the anterior lobe | 25% |
| Pituitary stalk resection | 3% |
| Infarct of the posterior lobe | 1% |

## 10.1.6 Timing of Onset

Hypothalamic-pituitary axis dysfunction may present at any time post ABI, and may change over time. Rates of hormonal imbalance or deficiency are highest in the acute phase. Typically, the rate of hormone abnormalities decreases as patients transition from the acute to the chronic phase of illness. Acutely, identifying ACTH deficiency and disorders of sodium balance due to ADH excess or deficiency are most important due to their high morbidity and mortality risk (Behan et al., 2008; Bernard et al., 2006; Hadjizacharia et al., 2008; Hannon et al., 2013; Maggiore et al., 2009).

The presence of neuroendocrine dysfunction acutely does not necessarily predict long-term hypothalamic-pituitary disorders. Many patients with early neuroendocrine disruption will recover this

function in the first 6 months post injury (Aimaretti et al., 2004a). In the acute phase after ABI, neuroendocrine dysfunction is estimated to affect 9% to 80% of persons who sustain a moderate to severe ABI (Agha & Thompson, 2005; Aimaretti et al., 2005; Barton et al., 2016; Bondanelli et al., 2004; Hannon et al., 2013; Hohl et al., 2014; Kleindienst et al., 2009; Kopczak et al., 2014; Lee et al., 1994; Olivecrona et al., 2013; Rosario et al., 2013; Schneider et al., 2006; Tanriverdi et al., 2007). Long-term, the prevalence of hypopituitarism has been estimated at 27-32% (Lauzier et al., 2014; Schneider et al., 2007b).

Although most hormone imbalances and deficiencies present in the acute phase of illness resolve over time, some patients may develop new hypothalamic-pituitary axis dysfunction in the chronic phase of illness. For instance, Ghigo et al. (2005) found that 5.5% of patients with no hormone deficiencies at 3 months developed them by 12 months post injury; these same authors found that 13.3% of patients with single axis deficiencies at 3 months developed multiple deficiencies at 12 months post ABI (Ghigo et al., 2005).

## 10.2 Signs and Symptoms of Neuroendocrine Dysfunction

**Q3. What neuroendocrine abnormalities should be monitored for in the acute post ABI period?**

Because they can be life-threatening, alterations in ACTH and ADH should be monitored:

1. ACTH deficiency can cause life-threateningly low levels of cortisol and can result in low blood sugar (hypoglycemia), low sodium (hyponatremia), and low blood pressure (hypotension).
2. ADH abnormalities can cause DI or SIADH and should be screened for by monitoring hydration levels, urine output, and serum sodium. DI can cause life-threatening increases in serum sodium, while SIADH can cause life-threatening reductions in serum sodium.

Neuroendocrine disturbances may present at any time following an ABI, and the presenting features vary by the hormone(s) affected. Single axis deficiencies, meaning hormones controlling one system, are more common than multi-axis deficiencies, in which two or more systems are affected. Single axis deficiencies are estimated to affect 30-40% of individuals with moderate to severe ABI, compared to 10-15% for multi-axis deficiencies (Aimaretti et al., 2004a; Benvenga et al., 2000; Kelly et al., 2000; Lieberman et al., 2001). Due to overlap in symptoms and signs, it may not always be possible to distinguish which hormones, if any, are affected clinically. These signs and symptoms can also overlap with the sequelae of an ABI in the absence of neuroendocrine dysfunction. Symptoms and signs of hormonal dysregulation for the most common pituitary hormone abnormalities are shown in Table 10.5.

**Common signs and symptoms of hypopituitarism include:**

- Fatigue
- Decreased cognitive function, concentration, and memory
- Mood disturbance, depression, and irritability
- Weight gain
- Decreased muscle mass and increased fat mass
- Sleep disturbance
- Amenorrhea, decreased libido, and/or erectile dysfunction

**Table 10.5 Features of Hypothalamic-Pituitary Dysfunction by Hormone Type**

| Hormone | Anterior Pituitary | | | | | Posterior Pituitary | |
|---|---|---|---|---|---|---|---|
| | **Low GH** | **PRL Excess** | **Low FSH/LH** | **Low TSH** | **Low ACTH** | **Low ADH**<br>*Diabetes Insipidus* | **ADH Excess**<br>*SIADH* |
| **Signs and Symptoms** | Sleep disturbance<br>Fatigue<br>Headaches<br>Depression<br>Muscle wasting<br>Reduced cognitive function<br>Reduced exercise tolerance<br>Increased abdominal fat<br>Reduced muscle mass<br>Dyslipidemia<br>Osteoporosis | *Women + Men*<br>Lactation<br>Breast enlargement<br>Decreased libido<br><br>*Women*<br>Altered or absent menses | *Women + Men*<br>Decreased exercise tolerance<br>Depression<br>Insomnia<br><br>*Women*<br>Altered or absent menses<br>Infertility<br>Decreased libido<br>Loss of pubic hair<br><br>*Men*<br>Decreased need to shave<br>Erectile dysfunction<br>Infertility<br>Decreased libido | Fatigue<br>Cold intolerance<br>Anemia<br>Muscle atrophy and cramping<br>Weight gain<br>Depression<br>Constipation<br>Loss of outer 1/3 eyebrow<br>Enlarged tongue<br>Coarse voice<br>Slow heart rate | Fatigue<br>Weakness<br>Muscle atrophy and cramps<br>Weight gain<br>Nausea<br>Vomiting<br>Anorexia<br>Hair loss<br>Low blood glucose | Polyuria (>3L of urine in 24 hrs, or >200 mL/hr for 2 hrs consecutive)<br>Polydipsia (severe thirst)<br>Orthostatic hypotension<br>Confusion<br>Altered mental status or coma<br>Seizures<br>High serum sodium | Anorexia<br>Nausea<br>Vomiting<br>Altered mental status or coma<br>Seizures<br>Low serum sodium |

Note: ADH=Antidiuretic hormone, ACTH= Adreno-corticotropin Releasing Hormone, FSH=Follicle Stimulating Hormone, GH=Growth Hormone, LH=Luteinizing Hormone, PRL=prolactin, TSH=Thyrotropin Stimulating Hormone

## 10.2.1 Anterior Pituitary Lobe Syndromes

Dysfunction of the anterior lobe of the pituitary gland can affect any of the anterior lobe hormones and the clinical features can vary widely depending on which hormone(s) is/are affected and how rapidly the dysfunction develops (Sandel et al., 2007). Anterior lobe dysfunction can start any time within 24 hours of injury to beyond 12 months post ABI (Agha et al., 2004; Agha & Thompson, 2005; Kelly et al., 2000; Nemes et al., 2015; Olivecrona et al., 2013). The clinical features associated with derangements of each of the anterior lobe hormones are outlined in this section.

### 10.2.1.1 Growth Hormone

GH, also known as somatotropin, serves a central role in growth and development in children. In adults, GH has roles in maintaining bone, muscle, and lipid metabolism. GH release is controlled by two hormones in the hypothalamus: growth hormone releasing hormone (GHRH), which promotes GH release from the anterior lobe, and somatostatin, which inhibits GH release from the anterior lobe. When released, one of the actions of GH is to stimulate the liver to produce IGF-1, which in turn acts on the many body tissues regulated by GH.

**Symptoms and signs of GH deficiency include:**

- Sleep disturbance, insomnia
- Fatigue, low energy
- Reduced exercise tolerance
- Low self-esteem
- Headaches
- Decreased cognitive function, concentration, and memory
- Depression
- Reduced lean body mass and muscle wasting
- Increased visceral adiposity
- Dyslipidemia
- Osteoporosis

Growth hormone deficiency is estimated to be one of the most common anterior lobe hormones affected by an ABI, affecting up to 30% of patients (Bondanelli et al., 2004; Hadjizacharia et al., 2008; Hannon et al., 2013; Olivecrona et al., 2013). The prevalence of GH deficiency post-ABI varies widely across studies from 2.8% to 63.6% (Agha et al., 2004; Agha & Thompson, 2005; Bondanelli et al., 2007; Kelly et al., 2000; Kopczak et al., 2014).

**Specific risk factors for GH deficiency include: older age and more severe injury** (Bondanelli et al., 2004; Kleindienst et al., 2009; Schneider et al., 2006; Tanriverdi et al., 2013). However, the clinical significance of GH deficiency in older age is disputed, as GH levels naturally decline with age and there are no well-established clinical benefits to replacement in normal aging (Cummings & Merriam, 1999). GH deficiency is also highly likely in patients with abnormalities in 3 or more hypothalamic-pituitary axes (Molitch et al., 2011).

#### 10.2.1.2 Prolactin

PRL is primarily responsible for stimulating lactation from the mammary glands. PRL production is stimulated by hypothalamic release of somatostatin and is inhibited by dopamine.

**Inadequate PRL Secretion: Hypoprolactinemia**

The incidence of low levels of PRL, or hypoprolactinemia, is estimated at <1-8% based on one study (Bondanelli et al., 2004). Low PRL after an ABI may result from injury to PRL-producing cells in the anterior lobe, or from dopaminergic medications used to treat sequelae of the ABI such as disorders of consciousness or movement disorders. Dopamine is a potent inhibitor of PRL release. The clinical significance and management of PRL deficiency following ABI has not been studied. Low PRL is not expected to be clinically significant in men; in women, there may be implications for lactation and menstrual cycles (Douchi et al., 2001). For childbearing and lactation concerns, referral to a reproductive endocrinologist could be considered.

**Excessive PRL Secretion: Hyperprolactinemia**

Excessive secretion of PRL, or hyperprolactinemia, may be present in 5-50% of patients following ABI, and may be clinically significant in 30% (Agha & Thompson, 2005; Aimaretti et al., 2004b; Bondanelli et al., 2005; Klose et al., 2007; Moreau et al., 2012). Elevated PRL levels can occur as part of the body's normal responses to critical illness, which is typically transient and likely of limited clinical significance (Behan et al., 2008). The prevalence of hyperprolactinemia post ABI may also be inflated by the commonplace use of antidopaminergic medications, which are known to increase serum PRL levels (Kilimann I et al., 2007; Kopczak et al., 2014). Hyperprolactinemia has not been shown to be associated with poorer patient recovery outcomes following ABI (Olivecrona et al., 2013). Importantly, some normal physiologic states, such as pregnancy or lactation, can cause high PRL levels, but these are not pathologic.

**Symptoms of hyperprolactinemia include:**

**In women:**

- Lactation
- Breast enlargement or pain
- Decreased libido
- Oligomenorrhea or amenorrhea

**In men:**

- Lactation
- Breast enlargement or pain
- Decreased libido

The causes of increased PRL secretion following an ABI are not well-elucidated. Antidopaminergic medications are thought to be a major contributor to the prevalence of elevated PRL (Kopczak et al., 2014; Schneider et al., 2006). Medications that are known to increase serum prolactin include: dopamine antagonists (antipsychotics), GABA-ergic medications, opiates, catecholamine depletors, and selective serotonin reuptake inhibitors (SSRIs). Elevated PRL can also result from structural causes, such as a pituitary adenoma or benign tumour. Patients with pituitary macroadenomas (large tumours) may experience headaches and a loss of their peripheral fields of vision, known as bitemporal hemianopsia, in addition to symptoms of hyperprolactinemia (Melmed et al., 2011).

#### 10.2.1.3 Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

FSH and LH are collectively known as gonadotropins, which are responsible for stimulating the gonads (ovaries and testes), regulating sexual development, sexual function, and fertility through the production of estrogen and testosterone. The levels of these hormones undergo natural variation over the life cycle, particularly with puberty, menstrual cycles, pregnancy, and menopause. The levels of FSH and LH can be measured directly from the blood, as can the end-products, estrogen and testosterone, which act on the hypothalamus in a negative feedback loop to regulate levels of FSH and LH.

Alterations along the hypothalamic-pituitary-gonadal axis are estimated to affect 13-80% of patients who experience an ABI, and can develop any time post injury (Hohl et al., 2009; Kopczak et al., 2014; Lee et al., 1994). In the acute period post injury, abnormalities along the hypothalamic-pituitary-gonadal axis can occur as part of the body's normal response to critical illness (Behan et al., 2008). The duration of FSH and LH deficiency is highly variable: some patients may experience spontaneous improvement, while others may experience persistent deficiencies up to and beyond 12 months (Agha & Thompson, 2005; Hohl et al., 2009; Hohl et al., 2018). Compared to patients without hypothalamic-pituitary-gonadal axis dysfunction, those with persistent hypogonadism may be more likely to experience poorer scores on the Functional Independence Measure, poorer scores on the Glasgow Outcome Scale, higher scores on the Disability Rating Scale, less clinical improvement on the Modified Rankin Scale, and poorer cognitive function (Agha & Thompson, 2005; Barton et al., 2016; Bondanelli et al., 2007; Schneider et al., 2006).

FSH and LH deficiency may produce osteoporosis, decreased exercise tolerance, reduced performance on memory and cognitive tasks, depression, and insomnia in both women and men (Hohl et al., 2009).

**FSH and LH deficiency may produce a number of symptoms related to sexual function in women and men, including:**

**In women:**

- Infertility
- Decreased libido
- Pubic and body hair loss
- Oligomenorrhea or amenorrhea

**In men:**

- Infertility
- Decreased libido
- Pubic and body hair loss
- Reduced facial hair growth
- Erectile dysfunction

As reviewed above, beyond fertility, there are important implications for recovery as well as prevention of morbidity associated with hypogonadism, such as osteoporosis; patients may benefit from seeing an endocrinologist.

#### 10.2.1.4 Thyrotropin Stimulating Hormone

TSH is released from the anterior lobe and acts on the thyroid gland, stimulating production of the thyroid hormones, triiodothyronine ($T_3$) and thyroxine ($T_4$). $T_3$ and $T_4$ act on nearly every cell in the body and are responsible for metabolism and growth. The serum levels of $T_3$ and $T_4$ also regulate metabolism by negatively feeding back on the hypothalamus, which then leads to less TSH production.

**Signs and symptoms of thyroid hormone deficiency, or hypothyroidism, include:**

- Constipation
- Fatigue, low energy, and exercise intolerance
- Cold intolerance
- Weight gain
- Anemia and pallor
- Muscle atrophy and muscle cramps; can cause myopathy and muscle weakness
- Bradycardia
- Hypertension
- Peri-orbital edema
- Loss of outer 1/3 of the eyebrow
- Macroglossia (enlarged tongue)
- Hoarse, deep voice
- Coarse, dry skin and thin hair
- Delayed relaxation of deep tendon reflexes
- Neuropsychiatric changes (depression, hallucinations, delirium)

In women, hypothyroidism can also cause menstrual cycle irregularities (more frequent, heavier menses). In rare, very severe cases, hypothyroidism can cause a myxedema coma, which is characterized by loss of consciousness (coma) and hypothermia.

Hypothyroidism is common in the general population, with a prevalence of 2-10% (Vanderpump, 2011). However, the vast majority of these patients have primary hypothyroidism, which is typically an autoimmune condition in which the thyroid gland does not produce enough $T_3$ and $T_4$, resulting in elevated TSH and low serum levels of $T_3$ and $T_4$ (Vanderpump, 2011). After an ABI, patients are at increased risk of developing secondary hypothyroidism, in which the pituitary gland's production of TSH is impaired resulting in low TSH and low serum levels of $T_3$ and $T_4$. This has important implications for diagnosing disorders of the hypothalamic-pituitary-thyroid axis after an ABI. Low or normal TSH alone is not adequate for screening or diagnostic testing of the hypothalamic-pituitary-thyroid axis (INESSS-ONF 2015).

Many studies have found that hypothyroidism due to TSH deficiency after an ABI is uncommon (Agha et al., 2005a; Agha et al., 2004; Behan et al., 2008; Kelly et al., 2000; Klose et al., 2007). However, if present, untreated hypothyroidism is associated with poorer cognitive outcomes (Moreau et al., 2012; Zetterling et al., 2013).

#### 10.2.1.5 Adrenocorticotropin-releasing hormone

ACTH is released from the anterior lobe of the pituitary gland and stimulates the adrenal glands to produce glucocorticoids, such as cortisol. ACTH release is regulated by corticotropin-releasing hormone, produced by the hypothalamus, and has a distinct diurnal pattern that produces the highest cortisol levels in the morning. ACTH secretion increases with stress, physical activity, and chronic disease. The hypothalamic-pituitary-adrenal axis has important roles in the body's response to stress and in regulating metabolism: in times of stress, the normal response involves increasing the production of ACTH and ultimately of cortisol. Because of its importance in the stress response, ACTH deficiency can be life-threatening (Behan et al., 2008; Bernard et al., 2006).

The number of patients who experience ACTH deficiency varies widely by study, ranging from 8.8-78% in the first week post ABI (Behan et al., 2008; Hannon et al., 2013; Olivecrona et al., 2013). ACTH deficiency is typically short-lived, but can persist 12 months or more from the time of injury (Behan et al., 2008; Ghigo et al., 2005; Kleindienst et al., 2009; Tanriverdi et al., 2013).

**The signs and symptoms of ACTH deficiency include:**

- Low blood pressure
- Hypoglycemia
- Low serum sodium (hyponatremia)
- Fatigue
- Weakness
- Nausea and/or vomiting
- Loss of appetite (anorexia)
- Hair loss
- Low quality of life

Importantly, patients with adrenal deficiency resulting from ACTH deficiency due to an ABI do not develop darkening of the skin, or hyperpigmentation. Hyperpigmentation is commonly seen in patients who have cortisol deficiency resulting from Addison's disease. In Addison's disease, cortisol deficiency results from failure of the adrenal glands to produce cortisol. These patients have high levels of ACTH as a result; when ACTH is produced, another hormone that darkens the skin is also produced. In patients who have cortisol deficiency due to an ABI, ACTH production is low so patients do not develop hyperpigmentation.

**Clinical Tip!**
In Addison's disease, patients with cortisol deficiency develop hyperpigmentation (darkening of the skin). This does not occur in ACTH deficiency from an ABI. Other features are similar in these conditions.

Adrenal insufficiency is diagnosed by testing morning cortisol levels, when cortisol is highest in patients with intact hypothalamic-pituitary-adrenal axis function. During the acute post-injury period, cortisol levels are expected to be high due to the heightened physiologic stress of an ABI; therefore, basal cortisol levels less than 7 ug/dL (193 nmol/L) or peak cortisol levels less than 20 ug/dL (550 nmol/L) may indicate adrenal insufficiency (Tanriverdi et al., 2006).

## 10.2.2 Posterior Pituitary Lobe Dysfunction

This section outlines disorders affecting the two posterior lobe hormones: oxytocin and ADH, also known as vasopressin. This section also details disturbances of salt and water balance which can present at any time post ABI but are most common in the acute period. These conditions include DI, which is due to inadequate ADH secretion, SIADH, which is due to excess ADH secretion, and Cerebral Salt Wasting (CSW), which is a rare condition affecting less than 1% of people with an ABI that also affects sodium but is not attributable to hypothalamic-pituitary axis dysfunction (Behan et al., 2008).

### 10.2.2.1 Oxytocin

There are no studies evaluating the incidence, prevalence, clinical significance, or management of oxytocin deficiency after ABI. Oxytocin stimulates uterine contractions during labour; if inadequate in this

setting, and for other clinical indications related to pregnancy, labour, and delivery, oxytocin supplementation is available (Leduc et al., 2013).

#### 10.2.2.2 Antidiuretic Hormone and Disorders of Sodium Balance

ADH regulates water balance in the body by acting on the kidney to promote the reabsorption of water in the renal tubules. In DI, inadequate secretion of ADH results in the production of large amounts of dilute urine, dehydration, extreme thirst, and high serum sodium (hypernatremia). In SIADH, excessive secretion of ADH results in the reabsorption of too much water, producing very concentrated urine and low serum sodium (hyponatremia). A summary of how to distinguish between disorders of sodium balance that may occur following an ABI is outlined in Table 10.6.

**Table 10.6 Distinguishing Disorders of Sodium Balance: Diabetes Insipidus, Cerebral Salt Wasting, and Syndrome of Inappropriate Antidiuretic Hormone secretion* (adapted from Rabinstein & Wijdicks 2003)**

| Clinical or Lab Feature | Diabetes Insipidus | Cerebral Salt Wasting | SIADH |
|---|---|---|---|
| **Serum sodium** | High (>145mmol/L) | Low (<135mmol/L) | Low (<135mmol/L) |
| **Urine sodium** | Variable | High (>20mmol/L) | High (>20mmol/L) |
| **Serum osmolality** | High (>290mOsm/L) | Low (<280mOsm/L) | Low (<280mOsm/L) |
| **Urine osmolality** | Low (<300mOsm/L) | High (>100mOsm/L) | High (>300mOsm/L) |
| **Total body volume (hydration status)** | Dehydrated | Dehydrated | Normal or excessive |
| **Blood pressure** | Low | Normal or low | Normal |
| **Hematocrit** | High | High | Normal |
| **Urine output** | Polyuria (>3L of urine per 24hr, or >200 mL/hr for 2+ consecutive hrs) | Polyuria (due to urinary loss of sodium) | Normal or oliguria |
| **Serum ADH** | Low (inappropriate) | High (appropriate) | High (inappropriate) |

*Laboratory values are provided for convenience based on normal reference values at St. Joseph's Health Care London and London Health Sciences Centre. Please consult your lab's normal values.
Note: SIADH=Syndrome of Inappropriate Antidiuretic Hormone secretion

Disorders of ADH and sodium balance are common following an ABI and are potentially life-threatening (Goh, 2004; Hannon et al., 2013; Maggiore et al., 2009; Makulski et al., 2008; Powner et al., 2006). In one study, DI was significantly associated with higher mortality in persons who sustain a TBI (Hannon et al., 2013) and in another study, DI was a leading cause of death in persons who sustained severe TBI (Maggiore et al., 2009). Similarly, SIADH after an ABI has been shown to be associated with adverse patient outcomes, including limited recovery and greater levels of disability (Moro et al., 2007).

#### 10.2.2.3 Hypernatremia: Diabetes Insipidus

DI results from inadequate secretion of ADH from the posterior lobe of the pituitary gland. DI causes the kidneys to produce large amounts of dilute urine (polyuria), resulting in dehydration, incredible thirst (polydipsia), and elevated serum sodium (hypernatremia). DI is estimated to affect 2-51% of patients following an ABI (Bondanelli et al., 2007; Born et al., 1985; Ghigo et al., 2005; Hadjizacharia et al., 2008; Hannon et al., 2013; Tsagarakis et al., 2005). Patients with more severe injuries, basal skull fractures, intraventricular hemorrhage, subarachnoid hemorrhage, or cerebral edema are at increased risk of DI

(Born et al., 1985; Hadjizacharia et al., 2008; Hannon et al., 2013). DI most commonly presents within the first week after an ABI (Hadjizacharia et al., 2008; Kelly et al., 2000). Often, DI presents in the early period after an ABI as a consequence of cerebral edema, and may resolve or improve over days to weeks as the swelling subsides (Agha et al., 2004). In other cases, DI may persist for months to years (Ghigo et al., 2005; Tsagarakis et al., 2005).

#### 10.2.2.4 Hyponatremia: SIADH and Cerebral Salt Wasting

Patients with an ABI may develop low serum sodium (hyponatremia) for a variety of reasons, including iatrogenically from medications and/or IV fluids, from adrenal insufficiency, or from SIADH and CSW. This section outlines the features of SIADH and CSW.

**Clinical Tip!**

Hypernatremia can also arise from the kidneys; this is known as nephrogenic diabetes insipidus. Consider nephrogenic DI in patients with high sodium not responding to desmopressin.

**Syndrome of Inappropraite Antidiuretic Hormone**

In SIADH, the posterior lobe of the pituitary gland produces abnormally high amounts of ADH. This causes excessive retention of water, resulting in low serum sodium (hyponatremia) and low serum osmolality due to dilution, and concentrated urine with high urine sodium and high urine osmolality.

**Patients with SIADH may present with a spectrum of signs and symptoms:**

- Low serum sodium (hyponatremia)
- If mild, low appetite (anorexia) with or without nausea and vomiting
- Altered mental status, ranging from restlessness or irritability to confusion to coma
- Seizures
- Increased body weight, cerebral edema, or peripheral edema

There are many potential etiologies for the development of SIADH after an ABI, including but not limited to direct consequence of the brain injury, medications, infections, respiratory illnesses such as pneumonia, and overtreatment of DI with ADH analogues (Agha et al., 2005b; Goh, 2004). The prevalence of SIADH after an ABI varies by study, ranging from 15 to 40% (Hannon et al., 2013; Moro et al., 2007). Risk factors for SIADH include subarachnoid hemorrhage and concomitant use of medications known to cause SIADH (Hannon et al., 2014).

**Table 10.7 Medications that Can Cause SIADH (Adapted from Shepshelovich et al. 2017)**

| Medication Class | Medications |
|---|---|
| **Antidepressants** | Citalopram, escitalopram, paroxetine, sertraline, duloxetine, venlafaxine, doxepin, mirtazapine, amitriptyline |
| **Antipsychotic agents** | Risperidone, haloperidol, quetiapine, chlorpromazine, olanzapine, fluphenazine, clotiapine, zuclopenthixol, perphenazine, thioridazine |
| **Anti-seizure agents** | Carbamazepine, phenytoin, valproate, lamotrigine, phenobarbital |
| **Neuropathic pain agents** | Pregabalin, duloxetine, venlafaxine |
| **Opioid pain agents** | Tramadol, oxycodone |
| **Chemotherapeutic and immunosuppressive agents** | Vincristine, cisplatin, cytarabine, busulfan, ifosfamide, cyclophosphamide |
| **Antidiabetic agents** | Glyburide |
| **Endocrine agents** | Desmopressin |

**Cerebral Salt Wasting**

CSW is a rare clinical condition resulting in low hydration status and blood pressure (hypovolemia) from excessive loss of sodium in the urine (Yee et al., 2010). Like SIADH, CSW produces hyponatremia (serum sodium <135 mmol/L) and high serum ADH levels (Yee et al., 2010). However, CSW is characterized by low hydration status, so the release of ADH is appropriate as the body is trying to restore normal hydration by concentrating urine and reabsorbing water (Table 10.6). In CSW, the dehydration results from the kidneys excreting too much sodium, which can produce large urine output (polyuria) despite high levels of ADH. Because CSW results in hyponatremia, the symptoms are similar to SIADH but patients may also experience clinical signs of dehydration, polyuria, significant thirst (polydipsia), low blood pressure, and salt cravings that can help distinguish them from SIADH (Rabinstein & Wijdicks, 2003; Yee et al., 2010).

## 10.3 Clinical Assessment, Screening, and Diagnosis

**Q5. What are the clinical features of neuroendocrine dysfunction that might indicate a need for testing?**

1. Fatigue, generalized weakness
2. Decreased cognitive function, concentration, and memory
3. Mood disturbance, depression, and irritability
4. Weight gain or loss, reduced appetite
5. Decreased muscle mass and increased fat mass
6. Sleep disturbance
7. Amenorrhea, decreased libido, and/or erectile dysfunction, reduced need for shaving facial hair

This section outlines the approach to identifying neuroendocrine dysfunction clinically and through screening tests, and arriving at a diagnosis. Figure 10.2 is an algorithm that outlines this approach.

### 10.3.1 Clinical Assessment

In the acute phase of after an ABI, patients should be monitored clinically for the development of signs and/or symptoms that suggest neuroendocrine dysfunction. In particular, patients should be monitored for signs or symptoms of adrenal insufficiency and DI, as these can have serious, life-threatening consequences (INESSS-ONF 2015). Routine screening for other neuroendocrine abnormalities during the acute period is not recommended due to the transient nature of some of these conditions, the potential risks and harms associated with over diagnosis and overtreatment, and due to the pitfalls of testing these hormones in the critically ill patient (Tan et al., 2017).

In patients who are in the subacute to chronic phases after an ABI, clinical assessment for the presence of signs and/or symptoms of neuroendocrine dysfunction should occur at a minimum of after 3-6 months post ABI (INESSS-ONF 2015). This requires screening for symptoms of neuroendocrine dysfunction, checking blood pressure, and, if appropriate or warranted, arranging for screening tests.

## 10.3.2 Screening Testing

In brief, the overlap with clinical sequelae of ABI, clinical features between neuroendocrine axes, and variability in timing of presentation have led to recommendations that patients with a history of moderate or severe ABI with features suggestive of hormone imbalance or deficiency at any time, or patients 3-6 months post injury, should have screening that checks multiple hormonal axes. Testing all patients with a history of mild TBI at 3-6 months is not recommended. The recommended tests are outlined in Table 10.8.

**Clinical Practice Guidelines for the Rehabilitation of Adults with Moderate to Severe TBI (INESSS-ONF 2015).**

*Screening of the hypothalamic pituitary axis should occur at 3-6 months post TBI or when symptoms are suggestive of a hormonal imbalance or deficiency. Screening should include:*

- *a.m. cortisol*
- *Serum glucose*
- *Thyroid hormone (Free T4)*
- *Thyroid-stimulating hormone (TSH)*
- *Prolactin, estrogen or a.m. testosterone (T)*
- *Follicle-stimulating hormone (FSH)*
- *Luteinizing hormone (LH)*
- *Insulin-like growth factor-1 (IGF-1).*

*Clinicians should be aware that a low or normal thyroid-stimulating hormone (TSH) does not rule out pituitary insufficiency with thyroid hormone deficiency.*

**For patients with disorders of sodium, such as hyponatremia (low serum sodium) or hypernatremia (high serum sodium), patients should be assessed for:**

- Hydration status
- Serum sodium
- Urine electrolytes
- Urine sodium

**Table 10.8: Screening Tests for the Hypothalamic-Pituitary Axes** (INESSS-ONF 2015)

| **Anterior Lobe** – these tests should be performed in the morning (before 9 am) | **Posterior Lobe** – patients' volume status/ hydration status should be checked along with: |
|---|---|
| Cortisol<br>Serum glucose<br>TSH and thyroid hormone (free T4)<br>PRL<br>Estrogen (women) or testosterone (men)<br>FSH<br>LH<br>IGF-1* | Serum sodium and urine sodium<br>Serum osmolality and urine osmolality |

*IGF-1 testing is controversial and may not need to be completed until all other neuroendocrine disorders are ruled out or at least 1 year post-ABI unless the patient has not reached skeletal maturity (Behan et al., 2008; Molitch et al., 2011; Sesmilo et al., 2007; Tan et al., 2017).

**Growth Hormone**

Testing for GH deficiency is recommended in patients who have experienced an ABI, particularly TBI or subarachnoid hemorrhage (Molitch et al., 2011). Screening for GH deficiency involves testing serum levels of IGF-1 (2016). If the IGF-1 level is low, further confirmatory testing is required; this may include provocative testing such as the insulin tolerance test or GHRH-arginine test (Molitch et al., 2011).

**Clinical Practice Guidelines for the Rehabilitation of Adults with Moderate to Severe TBI (INESSS-ONF 2015).**

*Individuals with TBI with an identified neuroendocrine abnormality on screening should be referred, where appropriate, to an endocrinologist familiar with this TBI population, particularly if stimulating testing may be required to further evaluate complex hormonal imbalance such as growth hormone (GH) deficiency and replacement.*

## 10.3.3 Diagnostic Testing

An approach to diagnostic testing for each of the anterior lobe and posterior lobe or sodium balance disorders are outlined in **Tables 10.9** and **10.10**, respectively. Many of the confirmatory or provocative tests outlined in this section should only be performed with adequate medical supervision due to the risks of potential adverse events, such as hypoglycemia, that may arise from testing. Referral to an endocrinologist is therefore recommended for provocative testing such as CRH stimulation test, insulin-induced hypoglycemia test, insulin tolerance test, and glucagon stimulation test.

**Table 10.9: Diagnostic Tests for Anterior Lobe Hypothalamic Pituitary Axis Dysfunction***

| **Hypothalamic-Pituitary Axis** | **Screening Test(s)** – should be performed before 9 am | **Abnormalities Indicating Need for Further Testing or Referral** | **Diagnostic Test(s) Indicating Abnormality** |
|---|---|---|---|
| Adrenal | A.M. cortisol<br>Serum glucose | Low cortisol (<7 ug/dL or 193 nmol/L)<br>Low glucose (<4 without other explanation) | A.M. cortisol <100 nmol/L is diagnostic<br>CRH stimulation test: cortisol <500 nmol/L<br>Insulin-induced hypoglycemia test: cortisol <500 nmol/L |
| Gonadal | LH<br>FSH<br>Estrogen (women)<br>Testosterone (men) | Low LH<br>Low FSH<br>Low estrogen<br>Low testosterone | Screening tests are sufficient for diagnosis; refer to endocrinologist |
| Prolactin | PRL | If low, consider referral if interested in lactation<br>If high, evaluate possible medication causes | Screening tests are sufficient for diagnosis<br>If no medication causes for hyperprolactinemia, consider referral |
| Thyroid | TSH<br>Free $T_4$ | Low TSH + Low $T_4$ | Screening tests are sufficient for diagnosis; consider thyroid hormone replacement +/- refer to endocrinologist |
| Growth Hormone** | IGF-1 | Low IGF-1 | Insulin tolerance test: GH <5.1 ug/L<br>Glucagon stimulation test: GH <3 ug/L |

*(Molitch et al., 2011; Tan et al., 2017)

**Although the GHRH-arginine test can be used as a diagnostic test for GH deficiency, this is not recommended in patients with a history of ABI as it may not be reliable (Molitch et al., 2011).

**FSH and Luteinizing Hormone**

Diagnosis of FSH and LH deficiency requires testing serum levels of FSH, LH, and estrogen (in women) or testosterone (in men). In premenopausal women, low estrogen levels in the absence of elevated FSH levels is diagnostic of hypothalamic-pituitary-gonadal axis dysfunction. In post-menopausal women, low estrogen levels can be normal; however, FSH and LH levels are expected to be high. In men, low testosterone levels in the absence of elevated LH is diagnostic of hypothalamic-pituitary-gonadal axis dysfunction.

**Hypothyroidism**

Diagnosing hypothyroidism in patients who have experienced an ABI requires testing serum TSH and free $T_4$ levels (INESSS-ONF 2015); both will be low if the patient has central hypothyroidism stemming from pituitary dysfunction.

**Table 10.10: Diagnostic Tests for Posterior Lobe Dysfunction and Disorders of Sodium***

| Condition | Screening Test(s) | Abnormalities Indicating Need for Further Testing or Referral | Diagnostic Test(s) Indicating Abnormality |
|---|---|---|---|
| DI | Simultaneous serum and urine sodium and osmolality<br>Urine output (mL/hr)<br>Clinical assessment of volume status | Serum sodium >145 mmol/L<br>Serum osmolality >290 mmol/L<br>Urine osmolality <300 mmol/L<br>Urine output >3L/24h, or >200 mL/hr for 2+ consecutive hours, or >5 mL/kg/hr<br>Dehydrated | Clinical assessment and screening tests are sufficient for diagnosis |
| SIADH | Simultaneous serum and urine sodium and osmolality<br>Clinical assessment of volume status | Serum sodium <135 mmol/L<br>Serum osmolality <280mmol/L<br>Urine osmolality >300 mmol/L<br>Normal volume status | Clinical assessment and screening tests are sufficient for diagnosis |
| CSW | Simultaneous serum and urine sodium and osmolality<br>Clinical assessment of volume status | Serum sodium <135 mmol/L<br>Serum osmolality <280mmol/L<br>Urine osmolality >300 mmol/L<br>Dehydrated | Clinical assessment and screening tests are sufficient for diagnosis |

*(Agha & Thompson, 2005; Capatina et al., 2015; Tan et al., 2017)

**Diabetes Insipidus**

Diagnosing DI requires assessing a patient's hydration status and urine output, measuring the serum sodium and urine sodium, and measuring the serum osmolality and urine osmolality. Patients with DI will appear dehydrated and yet will be producing large amounts of dilute urine (>3L of urine in 24 hours or >200 mL/hr for 2+ consecutive hours with low urine osmolality); serum sodium and serum osmolality will be abnormally high due to the large amount of water the patient is excreting in the urine from the absence of ADH. Measuring the serum ADH level is not required for diagnosis, but if measured will be low.

## 10.4 Management of Neuroendocrine Dysfunction

Neuroendocrine dysfunction can develop at any time following an ABI and can affect any component of the hypothalamic-pituitary axis. Limited evidence is available to guide treatment decisions in patients whose neuroendocrine dysfunction is secondary to an ABI. Wherever possible, management that is specific to the ABI population is provided; however, most of the treatments outlined in this section reflect management of central hypothalamic-pituitary axis disorders in the general population. Table 10.11 is a summary of the management for each hypothalamic-pituitary axis abnormality. Many of these conditions are most appropriately managed and monitored by an endocrinologist. Because spontaneous recovery can occur, clinicians should reassess periodically for the need of hormone replacement therapy.

**Table 10.11: Treatments for Diagnosed Hypothalamic Pituitary Axis Dysfunction**

| Hypothalamic-Pituitary Axis | Abnormality | Management | Notes |
|---|---|---|---|
| Adrenal | Low serum cortisol confirmed with CRH stimulation test | Hydrocortisone 50 mg q6-8h IM or IV (acute); 10 mg PO in the morning, 5 mg PO at lunch, and 5 mg PO in the early evening (long-term) | If suspected, do not delay initiating empiric treatment in the acute phase. |
| Gonadal | Low LH, low FSH, low estrogen (women) or testosterone (men) | Estrogen replacement<br>Testosterone replacement | Refer to endocrinologist to evaluate risks/benefits and monitor treatment |
| Prolactin | High PRL<br><br>Low PRL | Evaluate medications; consider cabergoline<br><br>- | Elevated PRL is normal in pregnancy and lactation.<br><br>Refer to endocrinologist if lactation concerns |
| Thyroid | Low TSH + low $T_4$ | Levothyroxine starting at 25-50 mcg daily (low dose) or 1.6 mcg/kg daily (full dose) PO | Target: free $T_4$ in middle to upper half of normal range; cannot monitor with TSH alone |
| Growth Hormone | GH deficiency | Recombinant GH 0.06 mg/kg subcutaneous three times per week | GH replacement is controversial in adults. |
| Diabetes Insipidus | Hypernatremia due to inadequate ADH | Desmopressin 0.1-0.4 mg/day intranasal or PO | |
| SIADH | Hyponatremia due to excessive ADH | Fluid restriction <1L/day<br>Consider adjunctive treatment with: TRH, hydrocortisone, ADH inhibitors (conivaptan) | Overcorrection of hyponatremia should be carefully avoided due to the risks of central pontine myelinolysis and osmotic demyelination syndrome |
| Cerebral Salt Wasting | Hyponatremia due to loss of sodium from kidneys | Rehydration with 0.9% NaCl, salt tabs, or hydrocortisone | |

**Growth Hormone**

GH replacement is recommended for persons who have GH deficiency and have not yet reached skeletal maturity (Molitch et al., 2011). In adults with an ABI and concurrent GH deficiency, several studies demonstrated some benefits to GH replacement (Devesa et al., 2013; Dubiel et al., 2018; Gardner et al., 2015; Hatton et al., 1997; Moreau et al., 2012; Mossberg et al., 2017). However, decisions around treatment are complex and patients should therefore be assessed by an endocrinologist to determine the appropriateness of treatment (Molitch et al., 2011; INESSS-ONF 2015).

**Prolactin**

Low PRL is not expected to be clinically significant in men; in women, there may be implications for lactation and menstrual cycles (Douchi et al., 2001). For childbearing and lactation concerns, referral to a reproductive endocrinologist could be considered.

Patients with elevated PRL should be evaluated for medications that may increase serum PRL levels (antidopaminergic medications); patients and healthcare providers should weigh the risks and benefits of discontinuing such medications with the severity of the patient's symptoms from elevated PRL. For patients with hyperprolactinemia secondary to medications, treatment is not required if asymptomatic (Melmed et al., 2011). For patients who are not on antidopaminergic medications, treatment with dopamine agonists such as cabergoline or bromocriptine and referral to an endocrinologist should be considered (Melmed et al., 2011).

Management of hyperprolactinemia varies based on the patient's preferences about the significance of their symptoms. Options include reassessment of any medications that may be increasing serum PRL which may need to be stopped. Consider MRI of the pituitary gland if concerned that hyperprolactinemia is the result of a pituitary adenoma. In patients with adenomas or elevated PRL not attributable to antidopaminergic medications, consider referral to an endocrinologist, who may consider treatment with dopamine agonists (Melmed et al., 2011).

**LH and FSH and the Hypothalamic-Pituitary-Gonadal Axis**

Management of patients with abnormalities along this axis depends patient preference, the significance of the patient's symptoms, and interest in fertility. Beyond fertility, there are important implications for recovery as well as prevention of morbidity, such as osteoporosis, associated with hypogonadism. Patients should also be evaluated for hyperprolactinemia, as elevated PRL can cause hypogonadism that resolves with correction of elevated PRL (Silveira & Latronico, 2013). Patients should be referred to an endocrinologist for consideration of testosterone replacement therapy or estrogen replacement therapy in men or women, respectively.

**Thyroid Hormone Deficiency**

Untreated hypothyroidism can lead to significant symptoms, abnormalities in other neuroendocrine axes, and is associated with poorer cognitive outcomes (Moreau et al., 2012; Zetterling et al., 2013). Hypothyroidism can be treated with thyroid hormone replacement using levothyroxine. Levothyroxine dosing can be initiated at full dose (1.6 mcg/kg/day) or at low dose (25-50 mcg/day) (Persani, 2012; Roos et al., 2005). Starting at low dose is recommended in patients who have concomitant cardiovascular disease or in whom clinicians are worried about side effects from medication administration (Roos et al., 2005). In patients with hypothyroidism secondary to an ABI, monitoring of the clinical response to thyroid replacement therapy requires checking free $T_4$ values (Persani, 2012); this is because TSH values do not accurately reflect the function of the hypothalamic-pituitary-thyroid axis in secondary hypothyroidism (INESSS-ONF 2015). The aim is to titrate the dose of levothyroxine to achieve a serum $T_4$ level that is in the middle to upper half of the normal range (Persani, 2012). Monitoring of $T_4$ levels should occur approximately every 6-8 weeks until therapeutic levothyroxine doses are achieved (Persani, 2012; Roos et al., 2005).

**Adrenocorticotrophic Hormone Deficiency and Adrenal Insufficiency**

Adrenal insufficiency can lead to life-threatening hypotension (which may be resistant to vasopressor support), hypoglycemia, and hyponatremia. In patients with suspected cortisol or ACTH deficiency in the acute phase of illness, treatment with hydrocortisone should start as soon as indicated (Tan et al., 2017). In the acute phase of illness, treatment with hydrocortisone 50 mg every 6-8 hours IV or IM is

recommended (Grossman, 2010; Tan et al., 2017). For long-term replacement, or for patients diagnosed as an outpatient, daily hydrocortisone dosed 10 mg in the morning, 5 mg at lunch, and 5 mg in the early evening is recommended (total daily dose 15-20 mg) (Grossman, 2010). Patients with adrenal insufficiency should also be advised regarding the need for increased doses in the event of illness (Grossman, 2010). With the support of an endocrinologist, patients should be monitored for signs and symptoms of over-replacement and for the spontaneous resolution of their ACTH deficiency.

**SIADH and Cerebral Salt Wasting**

Patients with hyponatremia from either SIADH or CSW require careful management, as hyponatremia is associated with significant potential risks: inadequate correction or correction that is too slow may lead to cerebral edema and possible permanent injury, while rapid correction or overcorrection increases a patient's risk of developing central pontine myelinolysis or osmotic demyelination syndrome (Diringer & Zazulia, 2006). Patients with acute hyponatremia and significant neurologic symptoms, such as altered level of consciousness, coma, cerebral edema, or seizures, should undergo more aggressive correction, but overcorrection should be strenuously avoided (Diringer & Zazulia, 2006). Diriginer & Zazulia (2006) recommend correcting serum sodium that is <125 mmol/L by 1 mEq/hour until the serum sodium reaches 125-130 mmol/L. Corrections should be much slower thereafter. For patients who are asymptomatic with hyponatremia, very slow correction using conservative measures should be the first line approach (Diringer & Zazulia, 2006). Because CSW and SIADH can be transient after an ABI, the need for ongoing treatment should be re-evaluated frequently.

For patients presenting with hyponatremia and a normal clinical volume status suggestive of SIADH, clinicians should evaluate the patient's medications (see **Table 10.7**) for possible contributing causes and consider initiating a fluid restriction, which is typically the mainstay of SIADH management. The precise volume of fluid restriction has not been established; several authors have previously suggested restrictions of 250-800mL per day (Born et al., 1985; Chen et al., 2014; Diringer & Zazulia, 2006; Doczi et al., 1982). However, fluid restriction may not be safe in patients who are hypovolemic, such as those with polytrauma, or in patients who are at high risk of cerebral artery vasospasm, such as those with a subarachnoid hemorrhage (Diringer & Zazulia, 2006). In these patients, fluid resuscitation with isotonic fluids or fluids with a greater tonicity than the patient's urine, or the use of ADH inhibitors, such as conivaptan, could be considered (Arai et al., 2009; Diringer & Zazulia, 2006; Moro et al., 2007). Thyroid Releasing Hormone (TRH) stimulation and treatment with hydrocortisone have also been described as effective for treating hyponatremia not responsive to a fluid restriction (Hannon et al., 2014; Moro et al., 2007; Zhang et al., 2010).

For patients presenting with hyponatremia and dehydration or low clinical volume status suggestive of CSW, clinicians should initiate isotonic fluid replacement (Diringer & Zazulia, 2006). In some patients, additional salt tabs, hypertonic fluids, loop diuretics, or hydrocortisone may be required (Hannon et al., 2014; Moro et al., 2007). Due to the pathophysiology of CSW, TRH supplementation is ineffective in correcting the serum sodium in this condition (Zhang et al., 2010).

**Diabetes Insipidus**

DI is among the most serious potential neuroendocrine complications of an ABI. The hallmark features of DI are polyuria, polydipsia (incredible thirst), signs of low intravascular volume status (such as hypotension), and hypernatremia from loss of water in the urine. For patients who are not conscious or

who cannot reliably indicate their thirst, arriving at a diagnosis requires monitoring of clinical volume status, serum sodium, and urine output (Capatina et al., 2015).

Once DI is confirmed using simultaneous testing of serum and urine sodium and osmolality, and volume status assessment, management of DI depends on the patient's level of consciousness and hemodynamic stability. For hemodynamically unstable patients, isotonic fluid resuscitation should occur along with administration of desmopressin (Capatina et al., 2015). Stable patients who are conscious with a high thirst drive in whom oral intake is safe should be encouraged to drink to thirst; if needed, treatment with desmopressin can be added if serum sodium and urine output are still high (Capatina et al., 2015). Stable patients who are conscious but not thirsty, or who are unconscious, should be given isotonic IV fluids or 5% dextrose with desmopressin (Capatina et al., 2015). Along with fluids to correct hypovolemia, desmopressin 0.4-1 mcg IV, SC, or intranasal can be administered once daily.

The aim of treatment is to slowly correct hypernatremia by no more than 10 mmol/L per 24 hours until serum sodium is <150 mmol/L and achieve a neutral fluid balance and normal volume status. Additional doses of desmopressin can be given as needed until these aims are achieved, with the goal of slowly correcting hypernatremia over time to avoid negative sequelae such as worsening cerebral edema (Capatina et al., 2015).

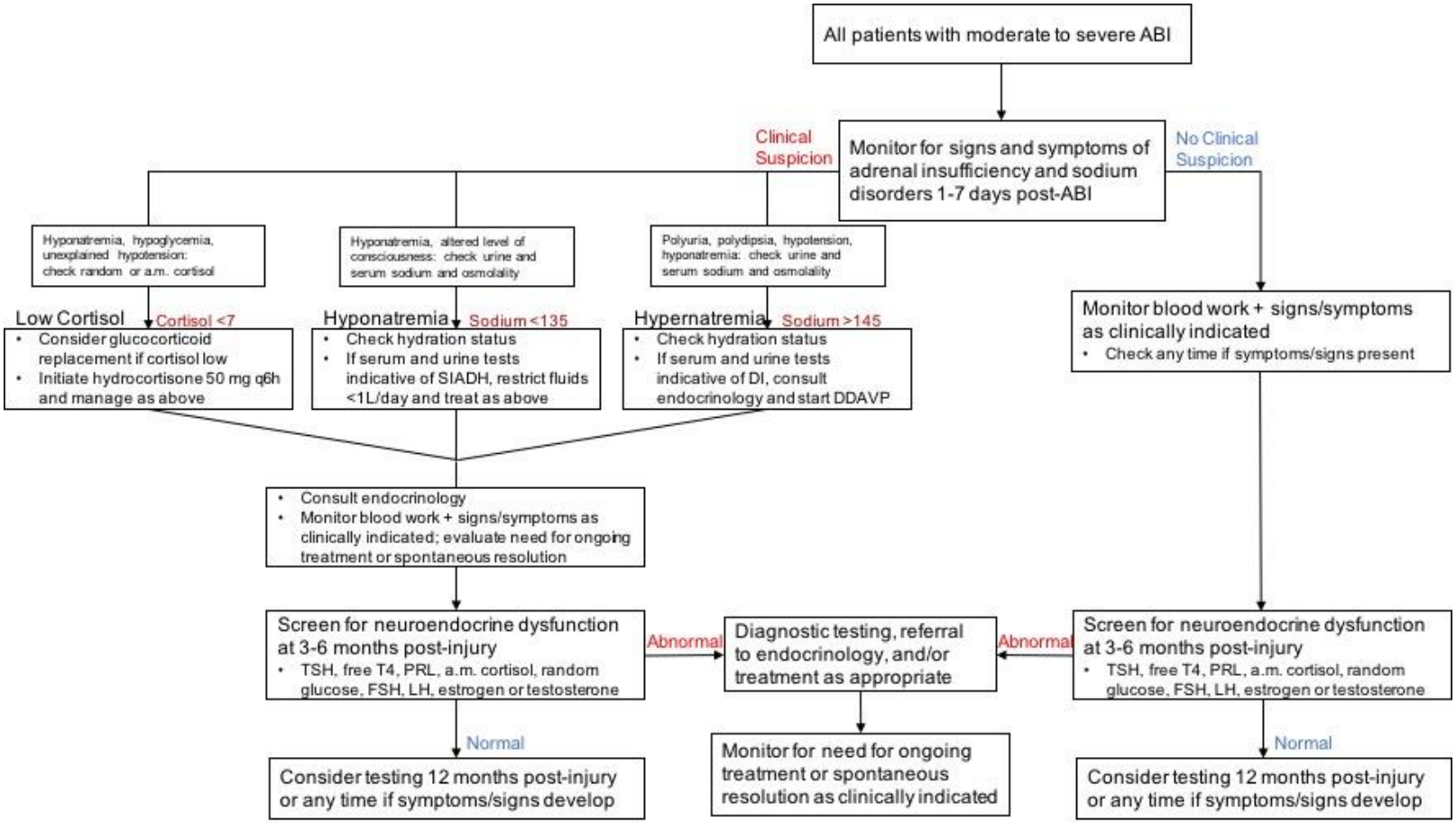


**Figure 10.2 Suggested Algorithm for Assessment of Neuroendocrine Function after ABI**

*Laboratory values are provided for convenience based on normal values at St Joseph's Health Care London and London Health Sciences Centre. Consult your own lab's normal values.

## 10.5 Summary

ABI can lead to dysfunction of the hypothalamic-pituitary neuroendocrine system directly or indirectly, and can affect the hypothalamus and/or the anterior, posterior, or both lobes of the pituitary gland. Neuroendocrine dysfunction presents with diverse signs and symptoms, can affect patients with any severity of ABI, can have potentially devastating negative consequences, and can present at any time post-injury. For these reasons, it is important for clinicians to have a high index of clinical suspicion for neuroendocrine dysfunction, and to consider screening for and treating neuroendocrine abnormalities at 3-6 months post injury and/or if signs or symptoms develop at any time. The clinical support of an endocrinologist can be invaluable in the management of this problem.

## 10.6 Case Study

### Patient Snapshot:

**Mr. J…**
Is a 42 year-old male who was involved in a high speed motor vehicle collision (MVC) resulting in a moderate brain injury and orthopedic injuries (fracture to his right tibia and fibula and right wrist) 3 months ago. He has been discharged home from hospital and is awaiting admission to an outpatient ABI Rehabilitation Program for further therapy.
**Lifestyle Factors:** Mr. J had a previous MVC (two years past) that resulted in a number of orthopedic injuries and chronic pain. He has completed a BSc and had just recently returned to work following recovery from the 1st MVC. He is recently single and has a supportive family who live in another city. He currently uses medical marijuana to manage pain and assist with sleep.
**Medical History:** Mr. J had an initial Glasgow Coma Scale score of 12, and his duration of post-traumatic amnesia was approximately four hours and has since resolved. An MRI has showed a diffuse axonal injury and cognitive screening at the time was suggestive of mild impairment. He had an open reduction and internal fixation for his tibia and fibula fractures and closed reduction of his wrist fracture. There is no history of alcohol or substance abuse, and he has chronic neuropathic pain.
**Signs & Symptoms:** Mr. J describes ongoing somatic pain symptoms in his right wrist and right leg that include pain with gripping and pain with walking; chronic headache; light and noise sensitivity; subjective impairment of memory and executive functions; low mood and easy irritability. At the time of your assessment, Mr. J expressed concerns about his level of fatigue, difficulty sleeping, and mood.

**Mr. J has been discharged from hospital and advised to follow-up with you. His brain injury was 3 months ago. What do you do next?**

**Review Mr. J's current medications.**
**Assess Mr. J for signs and/or symptoms of neuroendocrine dysfunction.**

***Note: Mr. J's neurobehavioural and motor/sensory impairment management is continued in the Neurobehavioral Case Study and Motor/Sensory Case Study which are part of Chapters 5 and 6 of this guidebook.**

**Q1. What are some questions to ask Mr. J to screen for neuroendocrine dysfunction?**

1. Have you experienced any unexpected or unexplained weight gain or weight loss?
2. Have you noticed changes in your energy levels, fatigue, or sleep?
3. Have you noticed a change in appetite, increased or severe thirst, or a change in urine output?
4. Have you noticed a change in how often you need to shave or new erectile dysfunction?

NB: in women, this last question should focus on changes in menstruation.

**Mr. J reports fatigue, poor sleep, low energy, and low mood are major issues for him.** He denies other significant symptoms suggestive of neuroendocrine dysfunction. On physical examination, Mr. J's blood pressure, heart rate, and clinical hydration status are normal. You record his weight, height, and body mass index, which is in the normal range. The remainder of his examination does not demonstrate any physical signs suggestive of neuroendocrine dysfunction.

**Q2. What assessments can you use to further examine the extent of Mr. J's symptoms?**

Mr. J is currently 3 months post ABI, so it is appropriate to screen for all neuroendocrine disorders at this time; however, some of the symptoms he is experiencing may not be attributable to neuroendocrine dysfunction.

**Screening tests should include:**

- Cortisol (morning/a.m. cortisol)
- Serum glucose
- TSH and thyroid hormone (free $T_4$)
- PRL
- Estrogen or testosterone (morning/a.m. testosterone)
- FSH
- LH
- Hydration status (assessed clinically, above)
- Serum sodium
- Urine electrolytes
- Urine sodium

Screening for GH deficiency by testing IGF-1 is controversial. You opt not to test IGF-1.

**You ask Mr. J to have blood work as an outpatient. Because of his fatigue, low energy, and recent surgery, you also test a CBC to rule out anemia. In addition, you assess his mood by performing a mental status examination and using the PHQ-9.**

Medications → Mr. J is using medical marijuana to help with sleep, mood and pain. He is also taking gabapentin.

Mood → On history and mental status examination, you identify that Mr. J has low mood; his PHQ-9 score is 9. You discuss options for mood management with him. At this time, he would like to wait for the results of the blood tests.

**Clinical Tip!**

TSH elevations are commonly seen in patients with serious illnesses or injuries, particularly in the acute phase. If the free $T_4$ is normal, no interventions are usually required.

Blood Work → Mr. J has blood work done at a lab in the community and you receive the results one week after you saw him. There are no concerning results that require calling Mr. J to direct him to go to the emergency department for urgent treatment. However, his cortisol level is slightly low: 135 nmol/L (normal reference range given is 138-600 nmol/L). His TSH is mildly elevated at 6.1 mU/L (normal reference range given is 0.4-5.5 mU/L). All of the other results are normal, including a normal free $T_4$, serum and urine sodium, and random glucose.

**Mr. J's blood work does not show neuroendocrine abnormalities. What do you do next?**

**You call Mr. J to provide him with the results over the phone.** You confirm that his blood work was taken in the morning. You explain that you would like to refer him to an endocrinologist to rule out adrenal insufficiency because of the low cortisol level. You also provide instructions to go to the emergency department if he develops signs of illness because of your concern about possible adrenal insufficiency. Mr. J expresses his understanding.

You ask Mr. J to return to see you for reassessment and to talk about next steps. You call an endocrinologist who works nearby to ask for an urgent appointment for Mr. J, and you fax a copy of the blood work results to the endocrinologist's office.

**Clinical Tip!**

For patients with suspected or known adrenal insufficiency, the risk of harm from adrenal crisis (severe adrenal insufficiency) is higher in illnesses (e.g., cold or flu), or in cases of surgery, vomiting, or serious injury (i.e., fracture). Counselling patients and their families/caregivers on what to do in these scenarios is important for their health.

**Q3. What will you caution Mr. J about as you wait for confirmation of adrenal insufficiency?**

Go to the emergency department for urgent evaluation if:
1. Symptoms of hypoglycemia: sudden unexplained sweating, anxiety, shaking, nausea, or palpitations.
2. Symptoms of illness such as cold or flu symptoms, vomiting, or diarrheal illness.

You are able to see Mr. J in follow-up a week later. He reports that there have been no significant changes in his symptoms. You re-check his heart rate, blood pressure, and clinical hydration status, which continue

to be normal. Because of his sleep dysfunction, you suggest a trial of melatonin. His appointment with the endocrinologist is next week.

**Mr. J has his appointment with the endocrinologist. Repeat cortisol testing does not show ongoing low cortisol levels, and CRH stimulation testing is normal. The endocrinologist informs you of the results and discharges Mr. J back to your care.**

You see Mr. J in follow-up 2-3 months later to check his progress. On history, his symptoms are unchanged. He denies new or worsening symptoms. He did not find the melatonin helpful and has discontinued this medication. You reassess his heart rate, blood pressure, weight, and BMI.

**You're following up with Mr. J three months after you screened for neuroendocrine dysfunction. What are your next steps?**

**At this time point, you want to reassess for new or worsening symptoms suggestive of neuroendocrine dysfunction and address other domains of concern such as fatigue and low mood. You can use reports from his therapy team and other specialists to add insight into his progress.**

Mr. J's symptoms have remained stable since you initially screened for neuroendocrine dysfunction. He has some vague symptoms that might be related to neuroendocrine dysfunction but these have not changed since you previously performed screening tests. These symptoms can also be attributable to non-neuroendocrine sequelae of an ABI. In discussion with Mr. J, you explain that you do not feel additional neuroendocrine testing at this time is necessary, and together you focus on addressing other areas of concern (See chapter 5 and chapter 6). You refer him to a psychiatrist and include the neuroendocrine work-up you have performed and the endocrinologist's note.

**Q4. Identify your 'successes' in managing Mr. J's care?**

1. You have successfully ruled out neuroendocrine causes for Mr. J's current symptoms.
2. You know his baseline weight, heart rate, and blood pressure so you can detect changes in future.
3. You have assessed and documented his symptoms so that you can detect changes in future.
4. You have communicated with other members of his care team to ensure a coordinated and safe management strategy

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