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

9. Neuroendocrine Function and Disorders Following Acquired Brain Injury

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Key Points

Syndrome of inappropriate antidiuretic hormone secretion may be effectively controlled with thyrotropin-releasing hormone (TRH) stimulation.

Growth hormone deficiency may be effectively treated with hormone replacement therapy and insulin growth like factor-1 therapy.

Progesterone may be effective in treating long-term outcomes in gonadotropic deficiency.

Table of Contents

Abbreviations

ABI	Acquired Brain Injury
ACTH	Adrenocorticotropic Hormone
ADH	Antidiuretic Hormone
DI	Diabetes Insipidus
GCS	Glasgow Coma Scale
GD	Gonadotropic Deficiency
GHD	Growth Hormone Deficiency
GHRH	Growth Hormone-Releasing Hormone
GnRH	Gonadotropin-Releasing Hormone
IGF-I	Insulin-Like Growth Factor I
LH	Luteinizing Hormone
MRI	Magnetic Resonance Imaging
PRL	Prolactin
PTHP	Post-Traumatic Hypopituitarism
RCT	Randomized Controlled Trial
SIADH	Syndrome of Inappropriate Antidiuretic Hormone
TBI	Traumatic Brain Injury
TRH	Thyrotropin-Releasing Hormone
TSH	Thyroid Stimulating Hormone

Neuroendocrine Function and Disorders Following Acquired Brain Injury

9.0 Introduction

Hypopituitarism is a common and treatable condition resulting from an acquired brain injury (ABI). Post-traumatic neuroendocrine disorders involving the pituitary gland can be divided into posterior or anterior pituitary dysfunction depending on which anatomical area is involved. This module explores the variety of disorders which can arise from neuroendocrine dysfunction and discusses relevant interventions. However, with the variety of disorders which can develop as a result of neuroendocrine dysfunction, specific ABI evidence is not always available, in these instances the most relevant research is discussed and provides an opportunity for further research.

9.1 Anatomy of the Pituitary Gland

The pituitary gland consists of two lobes derived from two different embryological pouches, the anterior lobe (or adenohypophysis) and the Posterior lobe (or neurohypophysis). The pituitary gland is connected to the hypothalamus through the pituitary stalk and controls both homeostasis and endocrine function.

The **anterior lobe** contains glandular cells which secrete hormones into circulation. It is controlled by the hypothalamus through the vascular portal system. The anterior lobe is responsible for the production of six important hormones, which are secreted into the circulatory system (Blumenfeld, 2002).

Figure 9.1 Diagram of the Hypothalamic Pituitary Axis

The **posterior lobe** contains the axons and nerve terminals of neurons which have their cell bodies in the hypothalamus. The hormones secreted by both the anterior and posterior pituitary and their target function are shown in Table 9.1. Following ABI, there may be notable changes in hormones released by the pituitary gland (Popovic et al., 2005).
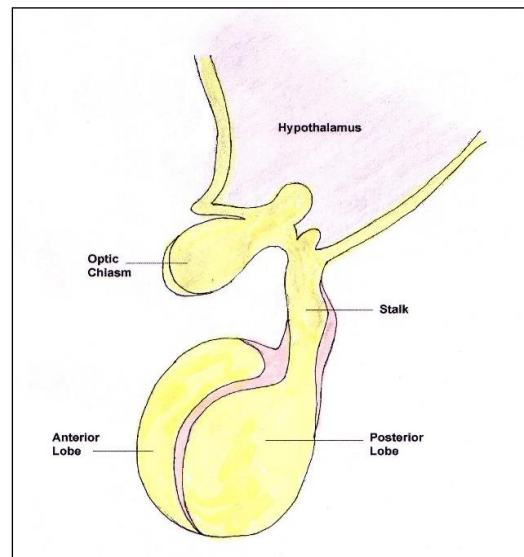
Table 9.1 Pituitary Hormones and Bodily Responses

Glands	Hormones	Part of Body Affected		Body Response
Anterior Pituitary	PL	Mammary gland		Lactation
	ACTH	Adrenal gland		Adrenaline
	GH	Body cells		Growth
	TSH	Thyroid		Stimulation of growth and metabolism
	FSH	Testes		Androgen production, sperm production, testosterone secretion
	LH	Ovaries		Ovum production, estrogen and progesterone secretion
Posterior Pituitary	ADH	Kidney		Water regulation
	Oxytocin	Uterus		Labour contractions

Note: ACTH=adrenocorticotropic hormone; ADH=antidiuretic hormone; FSH=follicle stimulating hormone; GH=growth hormone; LH=luteinizing hormone; PL=prolactin; TSH=thyroid stimulating hormone

9.1.1 History and Epidemiology

Neuroendocrine disorders, primarily hypopituitarism, were first diagnosed by the German researcher Cyran in 1918 (Benvenga, 2005; Lieberman et al., 2001; Makulski et al., 2008). Until recently, damage to the hypothalamus and pituitary gland following trauma was often not diagnosed until the post-mortem examination (Yuan XQ, 1991). Research indicates neuroendocrine disorders vary following traumatic brain injury (TBI) (Sandel et al., 2007), and what was once thought to be a rare occurrence is now increasingly diagnosed (Benvenga, 2005; Bondanelli et al., 2005; Ghigo et al., 2005). In the early 1950s, the incidence of hypopituitarism post injury was thought to be 1%; however, more recent rates have been quoted at between 20% and 70% (Makulski et al., 2008; Sirois, 2009). In a review of the literature, Schneider et al. (2007a) found that the pooled prevalence of hypopituitarism was 27% post TBI. The pituitary gland is most often affected with dysfunction occurring at the hypothalamic stalk or pituitary level.

Blood and urine analysis are the most common means used to diagnose neuroendocrine disorders. Disorders can be seen in the early days post injury, while the patient is still in the acute

stage of recovery, or in the later sub-acute stage. Overall, neuroendocrine abnormalities, hypopituitarism, and growth hormone deficiencies are common among those with TBI, especially those who have sustained moderate to severe injuries (Popovic et al., 2005). Figure 9.2 shows the pituitary gland under normal conditions and how it can be altered following a traumatic injury.

9.1.2 Signs and Symptoms

Neuroendocrine dysfunction may be observed as fatigue, temperature lability, disturbances in appetite, weight fluctuations, hypothalamic and pituitary disorders, disorders of fluid regulation, hypertension or hypotension, increased anxiety and depression, cognitive deficiencies, reduced bone and muscle mass, and immunologic disorders (Sesmilo et al., 2007; Sirois, 2009). Table 9.2 lists the clinical presentation of hypopituitarism.
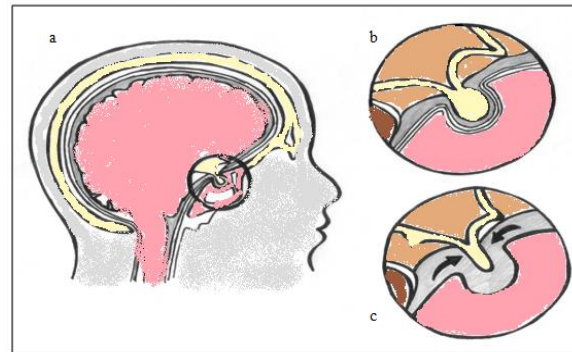
Figure 9.2 Pituitary Gland: Normal and Post-Traumatic Conditions

Table 9.2 Clinical Presentation of Hypopituitarism

- Fatigue
- Sleep disturbance
- Decreased muscle mass, increased fat mass
- Reduced exercise tolerance and muscle strength
- Amenorrhea, decreased libido, erectile dysfunction
- Decreased cognitive function, concentration, memory
- Mood disturbances, depression, irritability
- Social isolation, decreased quality of life

Neuroendocrine disorders post TBI result from specific injuries to the areas that regulate physiological functions in various regions of the brain, specifically injuries along the hypothalamic-pituitary axis (Sandel et al., 2007). Symptoms will vary depending on the area of the brain that has been affected by the injury. Current research suggests that anyone who suffers a brain injury (due to a stroke or TBI) and has a Glasgow Coma Scale (GCS) score between 3 and 12 should be tested for hormonal disorders or deficiencies (Behan et al., 2008). However, some extra attention should be paid in those patients with the most severe disability (i.e., vegetative state) (Sesmilo et al., 2007). Individuals at greatest risk for post-traumatic hypopituitarism (PTHP) are those who have sustained a diffuse axonal injury, a basal skull fracture, or who were older at the time of injury. Length of stay in the intensive care unit, longer hospitalization, and a prolonged loss of consciousness may also play a role in the development of hypopituitarism (Klose et al., 2007).

In the acute phase, very early hormonal alterations may reflect adaptive responses to injury and critical illness and are not necessarily associated with long-term PTHP. Various studies have shown that the majority of patients with low-grade or isolated deficiencies recover during the first 6 months post injury and tend to have a much better prognosis than those who do not recover (Aimaretti et al., 2004b; Bondanelli et al., 2004; Ghigo et al., 2005). In one study, 5.5% of patients who showed no signs of PTHP deficiencies at 3 months did so at 12 months. The same study showed that 13.3% of patients who demonstrated isolated deficiencies at 3 months developed

multiple deficiencies at 12 months (Ghigo et al., 2005). Growth hormone deficiency has been shown to be the most common deficit (Bondanelli et al., 2004; Ghigo et al., 2005).

Due to the nature of its features and the delay of its presentation, hypopituitarism may be missed following any type of ABI (Klionsky et al.) (Schneider et al., 2007a); thus, the diagnosis of hypopituitarism following an ABI remains a challenge. Some of the key indicators, such as low serum-like growth factor, may already be low in older patients due to normal aging. Studies examining this issue indicate that TBI severity, as measured by the GCS or EEGs, is not an accurate indicator of the likelihood of developing hypopituitarism. However, one study did show a non-significant trend to show an association with TBI severity (Sirois, 2009).

9.1.3 Association with Severity of ABI

There is no significant association between the development of PTHP and TBI severity, the type of accident, or the type of injury. While it has been shown by some researchers that PTHP patients had significantly lower GCS than unaffected survivors (Klose et al., 2007; Sirois, 2009), it has not been a consistent finding (Bondanelli et al., 2007; Ghigo et al., 2005). The incidence of skull fractures and neurosurgical procedures has been reported to be similar in patients with hypopituitarism when compared to those with normal pituitary function (Bondanelli et al., 2007).

Benvenga et al. (2000) have noted that PTHP is primarily a disorder seen much more often in male survivors between the ages of 11 and 39. This is likely related to the fact that young males tend to sustain head injuries most often. Currently there is no evidence that specific types of head injuries are more likely to lead to hypopituitarism (Ghigo et al., 2005). Due to the life threatening consequences associated with pituitary dysfunction, it represents a negative prognostic factor (Benvenga et al., 2000).

9.1.4 Diagnosis and Screening for Hypopituitarism

Diagnosis of neuroendocrine dysfunction is based on clinical evaluation, laboratory testing, and neuroimaging. According to Sesmilo et al. (2007) baseline hormonal testing should be performed in all patients, as described in Table 9.3. However, there is some dispute in the literature as to how soon after injury testing should be considered, how often it should be conducted, and who should be tested. As indicated previously, clinical assessment of hypopituitarism is difficult since the signs and symptoms are often nonspecific and mimic the neuropsychological sequelae of TBI. Thus, it is reasonable to consider performing baseline hormonal evaluation in patients with more severe injuries. Early on after injury, the most important anterior hormones to screen for may be thyroid stimulating hormone (TSH), growth hormone (GH), and Adrenocorticotropic hormone (ACTH) axes, as the dysregulation of these will more quickly lead to symptoms that can negatively affect recovery; although baseline testing of all hormones allows for easier follow-up.

Table 9.3 Hormonal Testing post ABI

Pituitary-Gonadal Axis	**Males:** LH, Follicle-Stimulating Hormone and testosterone **Females:** For those who have irregular menstrual cycles, LH, Follicle-Stimulating Hormone, and estradiol
Pituitary-Adrenal Axis	Cut-off values are different in the acute phase than in the rehabilitation phase. Evaluations are best performed with early morning plasma cortisol measurements or 24-hour urinary free cortisol measurements.
Pituitary-Thyroid Axis	It has been suggested that baseline testing should include thyroid function tests (TSH, fT_4, fT_3) and repetition of testing where appropriate.

Guidelines for screening patients who have sustained an ABI or a stroke for hypopituitarism include: severity of injury, location of injury (basal skull fractures, diffuse axonal injury, or increased intracranial pressure), GCS (especially scores between 3 and 12), length of time spent in the intensive care unit, and length of time post injury (Schneider et al., 2007b).

Given that hypopituitarism can evolve over time following injury, it is important to begin screening as soon as possible. In the acute stage, screening for adrenal insufficiency is particularly important due to its life threatening potential (Bernard et al., 2006). During the acute stage of recovery, cortisol levels of less than 7.2 μg/dL may indicate adrenal insufficiency. Another recent study has found that elevated levels of luteinizing hormone during early hospitalization are significantly associated with higher rates of mortality (Hohl et al., 2018) raising the importance of screening. Treatment should also be considered and initiated in cases where hyponatremia, hypotension, and hypoglycaemia are present, even if cortisol levels are between 7.2 and 18 μg/dL (Schneider et al., 2007a).

For those who have extended stays in the Intensive Care Unit and increased intracranial pressure, diffuse axonal injury, or basal skull fractures, assessing pituitary function should be considered. In the acute stage of recovery it is not necessary to assess growth, gonadal, or thyroid hormones as there is no evidence to suggest that supplementation of these hormones during this phase is beneficial (Ghigo et al., 2005; Schneider et al., 2007a); however, during the post recovery stage, at 3 and 6 months, a clinical assessment for hypopituitarism should be completed (Powner & Boccalandro, 2008; Powner et al., 2006; Schneider et al., 2007a). This is especially important if any of the following symptoms are noted: loss of secondary hair, impaired sexual function, weight changes, polydipsia, or amenorrhea.

Hormonal screening should include morning serum cortisol, fT_3, fT_4, TSH, Follicle-Stimulating Hormone, LH, Prolactin (PRL), Insulin-like Growth Factor (IGF-I), testosterone in men, and estradiol in women. In patients with polyuria or suspected DI, sodium and plasma osmolality and urine density should also be evaluated. Low IGF-I levels strongly predict severe growth hormone deficiency (GHD; in the absence of malnutrition). However, normal IGF-I levels may be found in patients with GHD as well; therefore, provocative tests are necessary in patients with another identified pituitary hormone deficit. Provocative testing is recommended if IGF-I levels are below the 25th percentile of age-related normal limits (Ghigo et al., 2005).

9.1.5 Neuroimaging

In a review of the literature, Makulski et al. (2008) concluded that magnetic resonance imaging (MRI) is the preferred imaging technique for the pituitary gland, as it can readily distinguish between the anterior and posterior lobes. MRI allows for both visualization of structural abnormalities and indirect imaging of the blood supply. The most common pathological findings are hemorrhage of the hypothalamus and posterior lobe, and infarction of the anterior lobe (Maiya et al., 2008; Makulski et al., 2008). While widely regarded as the best imaging technique, MRI may still fail to show pathological abnormalities in some patients with PTHP (Makulski et al., 2008).

Although neuroimaging (MRI or CT scans) can be successful in locating lesions within various sections of the brain, they do not reveal all pathology. Benvenga et al. (2000) found that 6% to 7% of those with PTHP showed no abnormalities on MRI. With regard to testing, blood tests remain the gold standard. Benvenga et al. (2000) suggested monitoring individuals for hypopituitarism if they are male and under the age of 40, have sustained their injury in a motor vehicle collision, and are within the first year post injury.

9.1.6 Provocative Testing

9.1.6.1 Growth Hormone Assessment

Approximately 20% of those with a TBI or subarachnoid hemorrhage are at risk for severe growth hormone deficiency (Klionsky et al.); provocative testing has been recommended in order to rule it out. Due to the expense of this test, it is recommended that other hormonal tests are conducted first, such as the IGF-I, , and that provocative testing is used only to rule out other transitory hormone deficits (Sesmilo et al., 2007). It is not recommended to use Insulin Growth Factor (IGF) levels as an assessment of overall growth hormone as multiple studies have found no association between the two (Bondanelli et al., 2005; Popovic et al., 2005).

9.1.6.2 Pituitary Function Testing (Serum Cortisol, ACTH)

The diagnosis of adrenocortical insufficiency requires provocative tests in addition to measurement of early morning basal serum cortisol levels. The normal basal morning serum cortisol values are between 150 nmol/L and 800 nmol/L (5.3–28.6 lg/dL). Basal morning serum cortisol <100 nmol/L (<3.6 lg/dL) is indicative of secondary adrenocortical insufficiency; if this value is >500 nmol/L (>18 lg/dL) adrenocortical insufficiency can be excluded. When basal serum cortisol values are borderline, a provocative test is necessary (Auernhammer & Vlotides, 2007).

9.1.6.3 Short ACTH Stimulation Test

In healthy subjects, stimulated serum cortisol has been shown to be between 550 nmol/L and 1110 nmol/L (19.6–39.6 lg/dL). Adrenocortical insufficiency is confirmed with a serum cortisol <500 nmol/L (18 lg/dL). Standard ACTH tests should be conducted at least 4 weeks after pituitary surgery (Auernhammer & Vlotides, 2007).

9.1.6.4 Insulin-Induced Hypoglycemia Test

During an insulin-induced hypoglycemia test, the top serum cortisol levels in healthy people are between 555 nmol/L and 1,015 nmol/L (19.8–36.2 lg/dL) (Auernhammer & Vlotides, 2007). Adrenocortical insufficiency is diagnosed when there is a serum cortisol increase of <500 nmol/L. Although this test has been shown to be the gold standard, caution is recommended when using the test, especially for the cardiac and epileptic patient where this test has been found to be contraindicated.

9.1.6.5 Metyrapone

Metyrapone has been shown to block the last step in the biochemical pathway between cholesterol and cortisol, leading to a reduction in serum cortisol, an increase of ACTH secretion and an increase of cortisol precursors such as 11b-deoxycortisol. The peak serum 11b-deoxycortisol levels in healthy people range between 195 nmol/L and 760 nmol/L. During the test, serum 11-deoxycortisol may increase to >200 nmol to exclude adrenal insufficiency. Another variant of the test is the ''multiple dose metyrapone test'', which requires other diagnostic cut-offs of serum 11b-deoxycortisol levels. In order to support this multistep testing, patients must be hospitalized. Metyrapone may cause gastrointestinal upset and may lead to adrenal insufficiency (Auernhammer & Vlotides, 2007). This test is considered only when other tests are inconclusive.

9.1.6.6 Corticotropin-Releasing Hormone (CRH) Test

Responses to this test vary widely between patients. Serum cortisol may increase to <350–420 nmol/L (<12.5–15 lg/dL) as evidence of secondary adrenocortical insufficiency, or it may increase to >515-615 nmol/L (18.5–22.0 lg/dL) excluding secondary adrenocortical insufficiency (Auernhammer & Vlotides, 2007).

Table 9.4 Tests of Pituitary Function (Auernhammer & Vlotides, 2007)

Tests	Methods
Growth Hormone test	• Assess family history: looking at age and weight related issues of individual and family members • Other pituitary deficits with normal IGF
Insulin-induced hypoglycemia test	• Insulin (0.1–0.15 IU/kg) intravenously sufficient to cause adequate hypoglycemia (<40mg/dL) (<2.2 nmol/L) • Blood samples are collected for measurement of serum cortisol at −15, 0, 30, 45, 60 and 90 min
Metyrapone test	• 30 mg/kg orally at midnight with a snack to minimize gastrointestinal discomfort • Blood for serum 11b-deoxycortisol, ACTH and cortisol are obtained at 8 AM
CRH test	• 100 µg recombinant human CRH is given intravenously • Blood samples for serum cortisol are collected at −15, 0, 30, 45 and 60 min
ACTH stimulation test	• 250 µg recombinant human ACTH and serum cortisol, given intravenously • Responses are assessed at 0, 30 and 60 min

9.2 Pathophysiology of Hypopituitarism Post ABI

9.2.1 Mechanism of Injury

An anterior pituitary infarction may be caused by compression of the pituitary gland, the hypothalamus, or interruption of the long hypophyseal vessels, which supply blood to the pituitary (Stanfield, 1960). This may be the result of direct trauma (i.e., skull fracture), edema, hemorrhage, elevated intracranial pressure, or hypoxic shock. Direct mechanical injury to the hypothalamus, the pituitary stalk, or the pituitary gland may also result in hypopituitarism. An infarction of the posterior lobe can be avoided if the inferior hypophyseal blood vessels are not transected when the pituitary stalk is ruptured. Diabetes insipidus (DI) often occurs as the result of inflammation and edema around the posterior pituitary gland; however, this has been shown to improve with time (Behan et al., 2008).

Potential lesions associated with TBI are shown in Table 9.5. The types of injuries and respective rates are listed below in Table 9.6.

Table 9.5 Hypothalamic-Pituitary-Adrenal Lesions Associated with TBI (Sirois, 2009)

Lesion	Causes of Injury	Location of Injury
Primary Lesion (direct)	Acceleration-deceleration	Traumatic lesion of the stalk
		Anterior lobe necrosis
		Posterior lobe hemorrhage
	Basal skull fracture	Direct lesion to pituitary, stalk, or hypothalamus
Secondary lesion (non-direct)	Brain edema	
	Hypoxia	
	Intracranial pressure	
	Hemorrhage	
	Inflammatory mediators	

Table 9.6 Type and Rate of Injury (Benvenga et al., 2000)

Type of Injury	Percentage
Hemorrhage of hypothalamus	29%
Hemorrhage of posterior lobe	26%
Infarction of anterior lobe	25%
Infarction of posterior lobe	1%
Stalk resection	3%

In 7% of cases, neuroendocrine disorders are not associated with neuroimaging abnormalities. The gold standard for neuroendocrine dysfunction includes serum tests assessing hormonal function (Benvenga et al., 2000).

9.2.2 Isolated and Combined Hormone Deficiencies

Although early hormonal abnormalities are not necessarily associated with long-term PTHP (Klose et al., 2007), the most common problem following ABI is a single axis or hormonal insufficiency. Research has shown that chronic hormone deficits occur in 30–40% of patients following ABI with

more than one deficiency occurring in 10–15% of the population (Aimaretti et al., 2004a; Bondanelli et al., 2004; Kelly et al., 2000; Lieberman et al., 2001). In general, single axis disturbances are more common than multiple axes disturbances (Krewer et al., 2016). Among individuals with an ABI, growth hormone deficiencies may be seen in 20% of those injured, gonadal hormone deficiencies in 15-30%, prolactin elevation in 30%, and hypothyroidism in 10–30% of the population. However, rates of hormonal deficiencies decrease dramatically from the acute to the post-acute phase, regardless of the number of axes impacted. Chronic adrenal insufficiency and DI post ABI occurs much more commonly, especially in those with a severe TBI (Bernard et al., 2006; Powner et al., 2006).

9.3 Disorders of Neuroendocrine Function and Available Interventions

9.3.1 Timing of Interventions

To date, there have been no published guidelines to advise when or how to treat endocrine dysfunction post ABI, including which medications to administer. It has been suggested that testing should begin immediately for those individuals who have been diagnosed with a moderate or severe ABI (Estes & Urban, 2005), and are no longer in a coma or vegetative state. Those who sustain diffuse axonal injuries may be at an even greater risk, regardless of injury severity, due to the rotational forces that the brain was subjected to (Estes & Urban, 2005). It is reasonable to repeat screening at a minimum of 6 to 12 months post injury and again at 18 and 24 months in those who with severe injury or early DI.

Conditions that require immediate treatment are dysfunction of ACTH, ADH, and TSH. GHD has been shown to improve with time and may improve as other deficiencies improve. As well, GHD treatment in the acute phase is not recommended, as there appears to be no benefit (Sirois, 2009). When there is clear indication of anterior or posterior pituitary dysfunction, consulting an endocrinologist is strongly recommended (Estes & Urban, 2005).

9.3.2 Interventions for Posterior Pituitary Dysfunction

9.3.2.1 Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Early studies investigating the impact of ABI on the posterior pituitary gland have demonstrated a disruption in sodium and fluid balance (Doczi et al., 1982). Makulski et al. (2008) noted that the more common medical consequences of acute TBI are disorders of salt and water balance resulting in syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyponatremia, and DI. Abnormalities of ADH represent one of the most common endocrine disturbances that occur in patients following TBI (Powner et al., 2006). SIADH has been diagnosed in patients when sodium serum levels drop below 135 mEq/L (hyponatremia) (Goh, 2004), coupled with an inappropriate elevation of urine osmolality (Blumenfeld, 2002).

Given that adrenal insufficiency can be life-threatening, it should be evaluated when it is suspected in the acute phase (Sesmilo et al., 2007). It is generally accepted that adrenal, thyroid, and gonadal function should be systematically studied 3-6 months after onset. Reassessment at 12 months should only be completed for those patients who had abnormal results at 3 to 6

months. Assessment for GHD should not be performed until other hormonal deficiencies have been managed (Sesmilo et al., 2007). It has been suggested that the use of medications such as carbamazepine, selective serotonin reuptake inhibitors (Li et al.), diuretics, vasopressin analogs, and chlorpromazine may lead to SIADH (Agha et al., 2005b; Goh, 2004; Haugen, 2009).

Table 9.7 Interventions for Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Zhang et al. (2010) China Pre-Post N=68	**Population:** Craniocerebral Injury (CI); Mean Age=27.8yr; Gender: Male=51, Female=17; Time Post Injury ≤24hr; Injury Severity: Mild=17, Moderate=18, Severe=33. **Intervention:** Patients hospitalized within 24hr of CI were assessed for post-injury hyponatremia, which was defined as blood [Na$^+$] <135mmol/L. Those with hyponatremia received thyrotropin-releasing hormone (TRH) stimulation. **Outcome Measure:** Incidence of hyponatremia, Level of ADH.	1. TRH stimulation was shown to mitigate symptoms of hyponatremia caused by SIADH by reducing blood ADH concentration from baseline to 60min post TRH stimulation (130.87±4.32 to 72.64±3.11pg/mL; $p<0.01$). 2. TRH stimulation was not effective in resolving hyponatremia caused by cerebral salt-wasting syndrome.

Discussion

Retrospective studies have identified a number of successful treatments for SIADH including intravenous saline (Chen et al., 2014; Moro et al., 2007), restricting fluid intake (Chen et al., 2014), hydrocortisone (Moro et al., 2007), and enteral urea (Annoni et al., 2016). In one prospective study, Zhang et al. (2010) reported that TRH stimulation mitigated the symptoms of hyponatremia caused by ADH, but did not resolve hyponatremia caused by cerebral salt-wasting syndrome, which is common in TRH stimulation. Thus, the effects of SIADH can be mediated by therapies that regulate levels of ADH and/or serum sodium.

When higher doses of sodium supplementation are found to be ineffective, hydrocortisone may be considered as treatment (Moro et al., 2007). These interventions may be administered alone or with loop diuretics (Arai et al., 2009). Conivaptan is a medication that has been approved to treat hypervolemic hyponatremia, although it has yet to be studied within the ABI population.

Findings suggest that while SIADH post injury is not overly common, it has a greater incidence among patients with severe injuries than those with moderate or mild injuries (Born et al., 1985; Doczi et al., 1982). The onset of SIADH may present as early as 2 to 3 days post injury (Born et al., 1985), but it may also persist beyond 12 months (Moreau et al., 2012). Depending on the diagnostic criteria, SIADH is recognized as "severe" if serum sodium is <125-130 mmol/L (Born et al., 1985; Doczi et al., 1982). Severe syndromes may be associated with poorer neurological function compared to moderate syndromes, and may require daily fluid restriction to resolve symptoms (Born et al., 1985). There is not a widely accepted target range for fluid restriction.

However, Doczi et al. (1982) suggested limiting daily fluid intake to less than 600-800mL, whereas Born et al. (1985) suggest limiting intake to 250-500mL.

Conclusion

There is level 4 evidence that TRH stimulation may be effective in treating hyponatremia post ABI.

Syndrome of inappropriate antidiuretic hormone secretion may be effectively controlled with thyrotropin-releasing hormone (TRH) stimulation.

9.3.2.2 Hyponatremia

Hyponatremia, defined as serum sodium concentration <136 mmol/L (Moro et al., 2007; Zhang et al., 2010), may result from SIADH or cerebral salt wasting (Moro et al., 2007). Symptoms of hyponatremia include lethargy, coma, or seizures. From three studies, the prevalence of hyponatremia post ABI ranged from 15% to 40% (Hannon et al., 2013; Moro et al., 2007; Zhang et al., 2010). Findings suggest that hyponatremia is more common in patients with severe, as opposed to mild or moderate, ABI (Zhang et al., 2010). Hyponatremia is undesirable during recovery as it is associated with longer administration days and worse outcomes at 1 month from treatment (i.e., limited 'good' recovery, higher number of patients with moderate disability) (Moro et al., 2007).

Recommendations for the management of hyponatremia resulting from SIADH include limiting daily fluid intake and TRH stimulation (Zhang et al., 2010). The former, in particular, directly decreases the level of circulating ADH in blood, and thus may represent an effective therapy for SIADH-induced hyponatremia. Its effectiveness, however, is limited against hyponatremia resulting from Cerebral Salt-Wasting Syndrome (Zhang et al., 2010) . Other ways to manage post-injury hyponatremia include IV or oral Na^+ supplementation . Higher dosages of Na^+ may be necessary if hyponatremia persists, and hydrocortisone should be considered if sodium supplementation is ineffective (Hannon et al., 2013; Moro et al., 2007). Moro et al (2007) reported that among patients with hyponatremia who did not respond to Na^+ supplementation initially, hydrocortisone therapy was initiated, and their serum Na^+ returned to normal range within 2 days of therapy. In conclusion, thyroid releasing hormone therapy, and sodium supplementation may be an effective treatment for managing hyponatremia.

9.3.2.3 Diabetes Insipidus (DI)

DI has been found to occur in patients with mild to severe TBI and can last from a few days to a month post injury (Tsagarakis et al., 2005). DI results in the production of large amounts of diluted urine. Post-injury DI may result from swelling around the hypothalamus or posterior pituitary but as the swelling begins to resolve itself so does the DI (Agha & Thompson, 2005). Individuals suffering from DI may experience polyphagia, polyuria, and polydipsia (Blumenfeld, 2002).

In general, post-ABI DI is an uncommon condition. In a large observational study by Hadjizacharia et al. (2008), 15% patients with either blunt or penetrating head injury were diagnosed with DI. In studies with smaller samples, the rates ranged from approximately 2.0% (Bondanelli et al., 2007; Born et al., 1985; Ghigo et al., 2005) to 14% (Bondanelli et al., 2004), while a single study finding DI among 51% of participants (Hannon et al., 2013). DI appears to have a relatively early onset, occurring within a week of injury (Kelly et al., 2000), or even within a few days (Hadjizacharia et al., 2008). While most studies suggest that post-injury DI is transient (Bondanelli et al., 2004; Hannon et al., 2013; Kelly et al., 2000; Schneider et al., 2006; Schneider et al., 2008), there is some evidence that DI may persist up to 3 months and even 12 months post injury (Ghigo et al., 2005). With regards to treatment, desmopressin has been shown to reduce urine output and liquid intake after head injury (Alaca et al., 2002; Born et al., 1985; Hannon et al., 2013).

Multiple risk factors for DI post ABI have been identified (Hadjizacharia et al., 2008). Multivariable analysis showed that patients with severe injury, brain edema, head Abbreviated Injury Score greater than or equal to 3, and/or intraventricular hemorrhage were at a greater risk of developing DI following ABI. There are suggestions that extensive fractures at the base of the skull may also be an important risk factor for DI (Born et al., 1985). Presence of DI may also predict deficiencies in other pituitary axes, such as hypogonadism (Schneider et al., 2008). Further, DI has been reported as significantly associated with higher mortality in individuals with TBI (Hannon et al., 2013), as well as a leading cause of death in those who sustain a severe TBI (Maggiore et al., 2009).

9.3.3 Anterior Pituitary Dysfunction and Available Interventions

Early research indicates that damage to the anterior pituitary was likely to be unreported post ABI in the past (Yuan XQ, 1991); however, anterior pituitary dysfunction is now increasingly recognized (Sandel et al., 2007). Anterior pituitary dysfunction may lead to a compromise in production of GH, TRH, PRL, glucocorticoid, and sex hormones (Sandel et al., 2007). Clinical presentation of anterior pituitary dysfunction varies widely, depending on the particular neuroendocrine axes affected, as well as the severity and rapidity of damage to that axis. The clinical presentation can range from subclinical disease to marked muscle or cardiovascular collapse (Sandel et al., 2007).

Several studies have examined the prevalence of anterior pituitary deficiencies following ABI. The rate varies widely across studies, ranging from 15.4% to 76.4% (Bondanelli et al., 2007; Hannon et al., 2013; Klose et al., 2007; Kopczak et al., 2014; Moreau et al., 2012; Nemes et al., 2015; Prodam et al., 2013; Rosario et al., 2013; Ulfarsson et al., 2013). The onset of anterior pituitary deficiencies may occur within 24 hours of injury (Olivecrona et al., 2013; Tanriverdi et al., 2007) and may persist up to 12 months post injury, and in some cases longer (Agha et al., 2005a; Agha et al., 2004; Bondanelli et al., 2007; Bondanelli et al., 2004; Ghigo et al., 2005; Kelly et al., 2000; Lieberman et al., 2001; Moreau et al., 2012; Nemes et al., 2015; Schneider et al., 2006).

Pituitary abnormality has been show to occur in one or more axes (Agha et al., 2004; Kelly et al., 2000; Klose et al., 2007; Kopczak et al., 2014; Lieberman et al., 2001; Schneider et al., 2006). However, there is no existing consensus as to which axis will be impacted or rendered impaired following an injury. For instance, impairments of growth hormone was seen in 100% (n=10) of patients with isolated deficiency in one study (Klose et al., 2007), another study only reported it

in 6% of patients (Lieberman et al., 2001). As well, Lieberman et al. (2001) reported that injury severity was not related to the number of affected pituitary axes.

Risk factors for anterior pituitary deficiencies following injury have been identified in a number of studies. Cuesta et al. (2016) reported that men with hypogonadism and women with menstrual dysfunction had more deficiency of various pituitary hormones than those without such conditions. Greater injury severity was found to be associated with post-injury hypopituitarism (Bondanelli et al., 2004; Klose et al., 2007; Nemes et al., 2015; Prasanna et al., 2015). In contrast, Tanriverdi et al. (2007) and Agha et al. (2004) did not find differences in pituitary dysfunction by injury severity. In other studies, high body mass index was found to be a risk factor for pituitary dysfunction (Klose et al., 2007; Ulfarsson et al., 2013). Further, Schneider et al. (2008) suggested that greater diffuse axonal injury and basal skull fracture are associated with a higher risk of pituitary impairment.

Outcomes of patients developing anterior pituitary dysfunction may be negatively impacted, whereby their ability to make good recovery post injury may be significantly reduced (Kelly et al., 2000). Marina et al. (2015) reported that Glasgow Outcome Scale Extended and Functional Independence Measure scores at both 3 months and 1 year were associated with elevated stress hormones as well as suppressed thyroidal and gonadal hormones. Similarly, Prasanna et al. (2015) found that lower Glasgow Outcome Scale Extended scores were associated with pituitary dysfunction, although Ulfarsson et al. (2013) did not find such results. As well, Rosario et al. (2013) reported that daily Functional Independence Measure gain was significantly lower in patients with hypopituitarism compared to those with normal function. However, the authors did not find any differences between those with and without endocrine function when comparing length of stay. Individuals with hypopituitarism have also been shown to have poorer Disability Rating Scores at discharge compared to those with normal function (Bondanelli et al., 2007). Prodam et al. (2013) found that individuals with hypopituitarism had higher prevalence of dyslipidemia and altered glucose metabolism.

In a systematic review (n=66), Lauzier et al. (2014) reported the prevalence, predictors, and clinical outcomes of anterior pituitary disorders following TBI. In the long term, 31.6% (n=27) of individuals were found to have at least one disorder. Predictors of these disorders were age (RR=3.19; n=19), injury severity (RR=2.15; n=7), and skull fractures (RR=1.73; n=6). As well, anterior pituitary disorders were associated with increased ICU mortality (RR=1.79; n=4), but not Glasgow Outcome Scale score (n=3).

9.3.3.1 Growth Hormone Deficiency

Although GHD is not uncommon following ABI, it is not as quickly diagnosed as other hormone deficiencies (Lieberman et al., 2001). GHD often escapes detection for months or years post injury. The signs and symptoms of GHD include fatigue, decreased muscle mass, osteoporosis, exercise intolerance, dyslipidemia, and truncal obesity, as well as a number of cognitive deficits and a poorer quality of life (Table 9.8)(Sandel et al., 2007; Schneider et al., 2007a).

Multiple findings suggest that higher body mass index is associated with a higher incidence of post-injury GHD (Agha et al., 2004; Lieberman et al., 2001; Schneider et al., 2006; Tanriverdi et al., 2013). Other predictors of GHD include low IGF-1 levels (Agha et al., 2005a; Agha et al., 2004;

Bondanelli et al., 2007; Lieberman et al., 2001; Olivecrona et al., 2013; Schneider et al., 2006; Tanriverdi et al., 2013), older age (Bondanelli et al., 2004; Schneider et al., 2006), and more severe injury (Kleindienst et al., 2009; Tanriverdi et al., 2013). Conversely, other studies have not found GHD to be associated with body mass index (Agha et al., 2005a; Aimaretti et al., 2005; Bondanelli et al., 2004) or injury severity (Agha et al., 2005a; Bondanelli et al., 2004).

Table 9.8 Clinical Presentation of Growth Hormone Deficiency

- Headaches, sleep disturbances, energy loss, fatigue, insomnia
- Attention/concentration disorders, decrease cognitive performance
- Irritability, depression
- Low self–esteem, poor quality of life
- Muscle wasting, decrease lean body mass, weight gain (visceral obesity)
- Decrease VO_2 max, decrease exercise tolerance, fatigability
- Atherosclerosis, osteoporosis, dyslipidemia

The prevalence of post-injury GHD varies considerably across studies, ranging from 2.8% to 63.6% (Agha et al., 2005a; Agha et al., 2004; Bondanelli et al., 2007; Bondanelli et al., 2004; Ghigo et al., 2005; Kelly et al., 2000; Kleindienst et al., 2009; Klose et al., 2007; Kopczak et al., 2014; Lieberman et al., 2001; Moreau et al., 2012; Schneider et al., 2006; Tanriverdi et al., 2007). As well, persistent deficiencies up to and beyond 12 months are commonly noted (Agha et al., 2005a; Agha et al., 2004; Bondanelli et al., 2004; Ghigo et al., 2005; Kelly et al., 2000; Kleindienst et al., 2009; Lieberman et al., 2001; Schneider et al., 2006; Tanriverdi et al., 2013).

In patients with a confirmed GHD, growth hormone replacement therapy has been recommended, and it is often administered subcutaneously (Auernhammer & Vlotides, 2007). The goal of therapy is to elevate serum IGF-I levels to at least the moderate range, which will vary depending on age and gender.

Table 9.9 Interventions for Growth Hormone Deficiency Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Dubiel et al. (2018) United States RCT PEDro=7 N=40	**Population:** Mean age=31.1yr; Gender: Male=34, Female=6; Mean Time Post-injury=64.1d. GCS: mild=4, Moderate=3, Severe=32, unknown=1. **Intervention:** Individuals were randomized to receive either recombinant human growth hormone or placebo. Follow-up was at 1-mo, 3-mo, 6-mo and 12-mo. 1-mo and 3-mo follow-up was only taken for IGF-1 concentrations. **Outcome Measure:** Disability rating scale scores (DRS), Functional Independence Measure (FIM) motor, FIM Cognitive, FIM total, IGF-1, Peak L-Arginine, California Verbal Learning Test (CVLT), Trail making test-A, Trail Making test-B.	1. At 3-mo and 6-mo follow-up the rhGH group had significantly higher IGF-1 concentrations (p=0.035, p=0.005), these were not observed at 1-mo or 12-mo follow-up. 2. At 6-mo follow-up the rhGH group had a significantly higher positive change in FIM motor scores (p=0.02), FIM cognitive scores (p=0.02), and total change in FIM scores (p=0.02). There were no other significant differences at 6-mo. 3. At 12-mo follow-up the rhGH group had maintained significantly higher positive scores in FIM motor scores

Author Year Country Study Design Sample Size	Methods	Outcome
		(p=0.02), and total FIM change (p=0.01).
[Hatton et al.](#) (1997) USA RCT PEDro=5 N=33	**Population:** TBI; *Intervention Group (n=17)*: Mean Age=27.6yr; Gender: Male=14, Female=3; Mean GCS=7; Mean Time Post Injury=56.5hr; *Control Group (n=16)*: Mean Age=27.8yr; Gender: Males=14, Females=2; Mean GCS=6.1; Mean Time Post Injury=57.1 hr. **Intervention:** Patients were randomly allocated to receive either continuous IV IGF-1 (0.01mg/kg/hr, treatment) or no IV treatment (control). IGF-I treatment began within 72hr of injury and continued for up to 14d. Both groups received nutritional support and neurosurgical intensive care. Patient assessments were made on 15d, 30d, discharge, and 3 and 6mo follow-up. **Outcome Measure:** Glasgow Outcome Scale (Klionsky et al.), Weight Loss, Glucose Concentrations, Nitrogen Balance.	1. IGF-1 treatment resulted in lower daily glucose concentration and nitrogen output (p=0.03) when compared to placebo. 2. Patients receiving IGF-1 treatment showed weight gain while those receiving placebo showed significant weight loss (p=0.02). 3. In patients with GCS=5-7, those receiving IGF-1 showed better outcome on GOS than those receiving placebo (p=0.06).
[Mossberg et al.](#) (2017) United States Pre-Post N=15	**Population:** TBI=15: Mean Age=45.5yr; Gender: Males=10, Females=5; Mean Time Post-Injury=11.2yr. **Intervention:** Daily injections of recombinant human growth hormone (rhGH) for 12 mo. **Outcome Measure:** Cardiorespiratory symptoms, Muscle force testing, Body composition, Cognitive function (BDI, Fatigue Severity Scale (FSS)).	1. There were no significant differences between pre and post measures of cardiorespiration (oxygen uptake, heart rate, minute ventilation, respiratory exchange ratio, oxygen pulse). 2. Although skeletal muscle fatigue did not decrease over the course of treatment, there was a strong trend for a decrease in perceived fatigue (p=0.06). 3. There was a strong trend for an increase in lean mass (p=0.06) post-treatment. 4. There was a significant improvement in both BDI (p=0.019) and FSS (p=0.039) scores post-treatment.
[Gardner et al.](#) (2015) Sweden Case Control N=1429	**Population:** *TBI (n=161):* Mean Age=42.6yr; Gender: Male=93, Female=68. *Tumour (n=1268):* Mean Age=53.2yr; Gender: Male=786, Female=482. **Intervention:** Participants diagnosed with GHD and treated with GH therapy were included in retrospective analysis. **Outcome Measures:** Quality of Life Assessment of GHD in Adults (QOL-AGHDA).	1. At baseline, mean QOL-AGHDA scores were significantly worse in the TBI group than in the Tumour group (p<0.0001) 2. After 1yr of treatment, mean improvement in QOL-AGHDA was greater in the TBI group than in the Tumour group (p=0.04), but the score remained worse in the TBI group. 3. Over 8 yr of treatment, mean improvement in QOL-AGHDA was

Author Year Country Study Design Sample Size	Methods	Outcome
		maintained in both groups, but the score remained worse in the TBI group.
Devesa et al. (2013) Spain Pre-Post N=12	**Population:** TBI; Mean Age=28.4yr; Gender: Male=8, Female=4; Mean Time Post Injury=5.3yr. **Intervention:** Participants received GH therapy (1mg/d, 5d/wk, 8mo) and clinical rehabilitation (3-4hr/d, 5d/wk, 6-12mo). Diagnosis of GHD was made by the following criteria: plasma GH <7ng/mL. **Outcome Measures:** Plasma IGF-1.	1. GHD was diagnosed in 42% of participants. 2. Before treatment, mean plasma IGF-1 levels were significantly lower in the GHD group than in the non-GHD group ($p<0.05$). 3. After treatment, mean plasma IGF-1 levels significantly increased in both the GHD group ($p<0.01$) and non-GHD group ($p<0.05$), such that the two groups were no longer significantly different ($p>0.05$). 4. Percentage increase in IFG-1 levels was significantly higher in the GHD group than in the non-GHD group ($p<0.01$).
Moreau et al. (2013) France PCT N=50	**Population:** TBI; *Intervention Group (TG, n=23):* Mean Age=37.9yr; Gender: Male=19, Female=4; Mean Time Post Injury=7.8yr; Mean GCS=8.1. *Control Group (CG, n=27):* Mean Age=37.1yr; Gender: Male=24, Female=3; Mean Time Post Injury=5.5yr; Mean GCS=9.4. **Intervention:** Participants were allocated to receive GH therapy (TG, 0.2-0.6mg/d) or no treatment (CG) for 1yr. GHD was diagnosed with an insulin tolerance test or GHRH assay. Outcomes were assessed before and after treatment. **Outcome Measures:** Quality of Life Brain Injury (QOLBI); Activities of Daily Living (ADL); Cognitive Function.	1. The TG showed significantly greater improvement in QOLBI functional ($p=0.023$) and personal ($p=0.019$) subscores. 2. No significant differences between groups were found for ADL or tests of cognitive function.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Recent research has found that growth hormone replacement therapy effectively elevates serum IGF-I levels in individuals with GHD post ABI (Devesa et al., 2013; Dubiel et al., 2018), as well as improves their quality of life (Gardner et al., 2015; Moreau et al., 2013). In a randomized controlled trial (RCT) of individuals with TBI, patients received IGF-I (5mg) via continuous intravenous infusion within 72 hours after injury and continued for 14 days, or placebo (Hatton et al., 1997). The authors found that patients receiving IGF-I treatment showed better outcomes in terms of glucose concentration, nitrogen balance, body weight, and recovery (Hatton et al.,

1997). In a more recent study, Mossberg et al. (2017) found that although recombinant human growth hormone did not improve respiratory capacity or symptoms, fatigue and depression scores significantly improved with treatment. Similarly, another RCT (Dubiel et al., 2018) found that more than just IGF-1 concentrations improved with recombinant growth hormone (rhGH) treatment. Cogntive and Motor Functional Independence Measure scores were seen to significantly increase in those receiving rhGH treatment at 6-month follow-up (Dubiel et al., 2018). These findings support the consensus that neuroendocrine dysfunction is a heterogeneous topic and treatment intervention may need to be tailored over time to an individual's specific needs.

Conclusions

There is level 1b evidence that growth hormone replacement therapy may improve clinical outcomes compared to placebo in patients with GHD post ABI.

There is level 4 evidence that growth hormone replacement therapy may be effective in treating GHD, fatigue, and depression post ABI.

> **Growth hormone deficiency may be effectively treated with hormone replacement therapy and insulin growth like factor-1 therapy.**

9.3.3.2 Gonadotropic Deficiency

Hypogonadism is often one of the earliest symptoms of hypopituitarism in those who survive a TBI (Lee et al., 1994). In males, it is important to monitor testosterone concentrations as low levels in the absence of elevated LH levels may indicate hypogonadism. In premenopausal women monitoring estradiol levels is important, as low levels of estradiol in the absence of elevated Follicle-Stimulating Hormone may be a sign of hypogonadism. Testosterone deficiencies in males and estradiol deficiencies in women may also be a sign of hypogonadism. In both genders, hypogonadism has been associated with sexual dysfunction, reduced vigour, mood disorders, insomnia, loss of facial, pubic and body hair, osteoporosis, and infertility (Hohl et al., 2009; Schneider et al., 2007a); a summary of these symptoms can be seen in Table 9.10.

Table 9.10 Clinical Presentation of Gonadotropic Deficiency

- Testosterone and estrogen/progesterone deficiency
- Hypogonadism: oligomenorrhea, amenorrhea, infertility, sexual dysfunction, decreased libido
- Muscle atrophy, osteoporosis, hair loss
- Reduced tolerance to exercise
- Decreased memory and cognitive performance

There is no consensus as to when to test for hypogonadism post injury. Due to uncertainty around the time when neuroendocrine disorders appear and disappear post injury, Hohl et al. (2009) suggested testing patients with TBI at least one year after injury for hypogonadism. Agha and Thompson (2005) suggested testing 3 to 6 months post injury, with follow-up testing at 12 months.

Gonadotropic deficiency (GD) is common among individuals with ABI, whereby acute prevalence rates range from 13% to 80% (Agha & Thompson, 2005; Aimaretti et al., 2005; Barton et al., 2016; 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). Persistent deficiencies up to and beyond 12 months have been commonly reported (Agha et al., 2004; Agha & Thompson, 2005; Aimaretti et al., 2005; Bondanelli et al., 2007; Bondanelli et al., 2004; Kelly et al., 2000; Kleindienst et al., 2009; Klose et al., 2007; Lieberman et al., 2001; Moreau et al., 2012; Schneider et al., 2006).

Common predictors of post-injury GD include older age (Agha et al., 2004), transient DI, polytrauma, hypoxia (Schneider et al.), and severe injury (Cernak et al., 1999; Kleindienst et al., 2009). Several studies found that GD was associated with poor GCS scores (Agha & Thompson, 2005; Cernak et al., 1999; Kleindienst et al., 2009; Schneider et al., 2006), although other studies have not reported this relationship (Bondanelli et al., 2007; Tanriverdi et al., 2007). Compared to individuals with normal hormone functioning, GD was also found to be associated with poorer scores for the Functional Independence Measure, Disability Rating Scale, cognitive function (Barton et al., 2016; Bondanelli et al., 2007), and Glasgow Outcome Scale scores (Agha & Thompson, 2005; Barton et al., 2016). GD was also correlated with lower Functional Independence Measure gains per day (Rosario et al., 2013) and less clinical improvement on the modified Rankin Scale (Schneider et al., 2006). However, one study reported that the rate of GD did not differ between individuals who survived and did not survive (Tanriverdi et al., 2007).

Androgen Replacement in Men or Testosterone Therapy

Treatments for hypogonadism in men include oral testosterone replacement therapy, subcutaneous implantation (3-6 pellets of 200mg unmodified testosterone every 4-6 months), intramuscular injections (testosterone esters), transdermal patches and gels, and buccal delivery (Nieschlag et al., 2004). Although several treatments are available and there are several evidence-based guidelines on when and how to treat hypogonadism, there is no literature on the effectiveness of these treatments within the ABI population.

Estrogen Replacement in Women

Hormone replacement therapy in women has been shown to be effective during their menopausal or perimenopausal years. However, long-term treatment is not recommended due to the negative benefit-risk ratio (Auernhammer & Vlotides, 2007). Other treatments for women may include the administration of daily dehydroepiandrosterone or testosterone. Although some success has been found using these treatments, neither has been studied within the ABI population.

Table 9.11 Progesterone Interventions Post ABI

Author/Year/ Country/Study Design/N	Methods	Outcome
Soltani et al. (2017) Iran RCT	**Population:** *Experimental Group (n=20)*: Mean age=27.85yr; Mean GCS=7.7. *Control Group (n=24)*:	1. There were no significant differences between groups at 3 mo post-trauma based on treatment. However, at 6 mo post-trauma the

PEDro=7 N=48	Mean Age=30.37yr; Mean GCS=7.7. **Intervention:** 1 mg/kg of Progesterone was given intramuscularly every 12 hours for 5 days to the experimental group, while the control group received no treatment. Participants received treatment within 12 hours of initial trauma. **Outcome Measure:** Glasgow Outcome Scale-Extended (GOS-E), Functional Independence Measure (FIM), serum progesterone levels, mortality.	progesterone group had significantly higher GOS-E scores (p=0.03), with only 1 death in the progesterone group compared to 7 in the control group. 2. FIM scores showed a similar trend with no significant difference between groups at 3 mo but 6 mo post-trauma the progesterone group had significantly higher FIM scores (p<0.05). 3. At baseline there was no significant difference between groups in terms of serum progesterone levels, however after the initiation of treatment the progesterone group maintained significantly higher progesterone levels until the end of the trial (p<0.05). 4. The control group experienced significantly higher mortality compared to the progesterone group (p<0.05).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In a RCT, progesterone treatment did not appear to improve functionality short-term (<3 mo), however at 6mo follow-up patients had significantly higher Glasgow Outcome Scale Extended and Functional Independence Measure scores (Soltani et al., 2017) . Furthermore, the control group experienced significantly higher mortality than the progesterone group. In contrast to these results, a systematic review of 5 studies concluded that there are no sure benefits to progesterone administration compared to placebo (Ma et al., 2016). Authors consistently found no difference between disability or mortality between groups.

Conclusion

There is level 1b evidence that progesterone treatment improves long-term outcome and functionality, but results may not be observed short-term in ABI populations.

Progesterone may be effective in treating long-term outcomes in gonadotropic deficiency.

9.3.3.3 Hyper/Hypoprolactinemia

Hyperprolactinemia has been shown to be present in more than half of patients with ABI in the early acute phase and it is believed that approximately 30% of patients show symptoms (Bondanelli et al., 2005). Kilimann et al. (2007) found males had higher levels of PRL than females and more males were found to have hyperprolactinemia than females. However, it should be noted that all patients with hyperprolactinemia also had an infection, were hypoglycemic, or were on medications known to increase PRL levels (dopamine antagonists, GABA agonists, opiates or central catecholamine depletors).

The rate of post-ABI hyperprolactinemia varies widely across studies, ranging from 5% to 50% (Agha et al., 2005a; Aimaretti et al., 2005; Bondanelli et al., 2004; Kleindienst et al., 2009; Klose et al., 2007; Kopczak et al., 2014; Lieberman et al., 2001; Moreau et al., 2012; Olivecrona et al., 2013; Schneider et al., 2006; Tanriverdi et al., 2007). It is important to note, however, that the rate of post-injury hyperprolactinemia may be lower if patients receiving hyperprolactinemia-inducing drugs are excluded from the analysis (Kopczak et al., 2014; Lieberman et al., 2001; Schneider et al., 2006). Based on a limited number of studies, the rate of post-ABI hypoprolactinemia ranged from <1% to 8% (Bondanelli et al., 2004).

Post-injury hyperprolactinemia may persist up to 12 months post injury (Agha et al., 2005a; Ghigo et al., 2005; Kleindienst et al., 2009; Schneider et al., 2006). However, it is difficult to predict whether individuals sustaining ABI will develop hyperprolactinemia. Agha et al. (2005a; 2004) reported that post-injury hyperprolactinemia was not associated with factors such as age, sex, or GCS score; although a later study reported that GCS scores were negatively correlated to post-injury PRL levels (Tanriverdi et al., 2007). Given the apparent lack of association with negative outcomes, hyperprolactinemia may not be a significant deterrent to patient recovery (Olivecrona et al., 2013).

9.3.3.4 Adrenocorticotropic Hormone Deficiency

ACTH secretion tends to fluctuate at night and increase with stress, physical activity, and chronic disease. Cortisol levels taken in the morning are low and there is a poor cortisol response to ACTH stimulation (Sandel et al., 2007). The signs and symptoms of ACTH deficiency are listed in Table 9.12 (Schneider et al., 2007a).

Table 9.12 Clinical Presentation of Adrenocorticotropic Hormone Deficiency

- Fatigue, weakness, anorexia, nausea, vomiting
- Hair loss
- Low blood pressure
- Hypoglycemia
- Absence of hyperpigmentation
- Poor quality of life
- If acute, may be life-threatening

Findings from multiple studies suggest that ACTH (or cortisol) deficiency within 1 week of injury can vary considerably in rate, ranging from 8.8% to 78% (Hannon et al., 2013; Olivecrona et al., 2013). It is suggested that injury severity is an important predictor of ACTH deficiency, whereby more severe injuries are associated with more frequent or more profound ACTH deficiencies (Kleindienst et al., 2009; Tanriverdi et al., 2013; Tanriverdi et al., 2007). Other factors may include older age, injury to the basal skull, and lack of cranial vault fracture (Schneider et al., 2008). It has also been noted that women with menstrual dysfunction post ABI have significantly higher ACTH compared to those that have no menstrual dysfunction (Cuesta et al., 2016). However, there are inconsistencies as to whether these factors do in fact play a role in inciting post-injury corticotropic complications (Agha et al., 2005a; Agha et al., 2004; Bondanelli et al., 2007; Olivecrona et al., 2013).

Individuals living with ABI may continue to demonstrate post-injury ACTH deficiency for up to 12 months (Ghigo et al., 2005) and beyond (Kleindienst et al., 2009; Tanriverdi et al., 2013). This may

be problematic for recovery, as post-injury ACTH deficiency has been shown to be associated with poorer cognitive and physical outcomes (Moreau et al., 2012), as well as with other anterior pituitary disturbances such as hyperprolactinemia, low testosterone, and low tT_3 and fT_4 (Kleindienst et al., 2009), and higher mortality (Hannon et al., 2013). Further, there is a lack of known treatment options available to manage post-injury ACTH deficiencies.

9.3.3.5 Thyroid-Stimulating Hormone Deficiency

TSH deficiency appears to be less common than other hormonal deficiencies post ABI (Schneider et al., 2007a). Reduced thyroid function may lead to a decrease in an individual's basal metabolic rate and cognitive function, and an increase in fatigue (Elovic, 2003). In children, TSH deficiencies may lead to growth retardation (Alexopoulou et al., 2004). The signs and symptoms of TSH deficiency are listed in Table 9.13, many of which do not present until much later in the recovery period (Schneider et al., 2007a).

Table 9.13 Clinical Presentation of Thyroid-Stimulating Hormone Deficiency

- Constipation
- Fatigue, paleness, cold intolerance
- Muscle atrophy, muscle cramps, weight gain, myopathy
- Coarse voice, macroglossia
- Bradycardia, hypotension, anemia
- Anemia
- Pre-orbital edema
- Neuropsychiatric disorders (hallucinations, delirium)

Diagnosing TSH deficiency has been shown to be more difficult, as the symptoms are often masked by other hormonal deficiencies post ABI. The treatment of TSH deficiency is often with levothyroxine (Yamada & Mori, 2008).

Multiple studies found that post-ABI TSH deficiency is uncommon, with very few individuals displaying symptoms at or greater than 6 months post injury (Agha et al., 2005a; Agha et al., 2004; Bondanelli et al., 2007; Kelly et al., 2000; Klose et al., 2007). Impaired thyrotropic function is undesirable from a recovery standpoint, as a trend toward poor cognitive outcome was observed in individuals with thyrotropic dysfunctions (Moreau et al., 2012; Zetterling et al., 2013).

Findings by Kleindienst et al. (2009) suggest that more severe injuries are associated with greater incidence of low TSH and fT_4 levels, and thus post-injury thyrotropic complications. Earlier findings by Cernak et al. (1999) demonstrated that individuals with severe TBI had more profound thyrotropic disturbances than those with mild TBI. More specifically, those with severe TBI had decreased TSH levels for the entire duration of the study (7 days), whereas those with mild TBI showed an elevated TSH response for only a few days post injury. These findings are inconsistent with Tanriverdi et al. (2007), who reported that no significant differences in mean TSH levels were found among individuals with mild, moderate, and severe injuries. The discrepancy across studies indicates that there is still considerable uncertainty regarding predicting outcomes for those with post-injury thyrotropic complications (Moreau et al., 2012).

9.4 Conclusions

The prevalence of neuroendocrine dysfunction varies considerably among studies and this may reflect the inaccuracy of testing methods. Neuroendocrine disorders often result in a variety of symptoms including temperature lability, appetite disturbances, decreased muscle mass, sleep disturbances, hair loss, decreased libido, and disorders of fluid regulation, or hypertension (Sirois, 2009). With the exception of DI, other neuroendocrine disorders remain underreported and underdiagnosed. Testing should be conducted while the patient is in acute care for ACTH and ADH deficiencies and then during the next 12 months for the remaining hormones. Failure to identify these dysfunctions could impact the individual's recovery process and impact their overall quality of life. Overall the current state of research-based evidence for many neuroendocrine dysfunctions is lacking. There needs to be a specific focus in research to determine the potential interventions available to ABI populations as neuroendocrine disorders are often neurogenic.

9.5 Summary

There is level 4 evidence that TRH stimulation may be effective in treating hyponatremia post ABI.

There is level 1b evidence that growth hormone replacement therapy may improve clinical outcomes compared to placebo in patients with GHD post ABI.

There is level 4 evidence that growth hormone replacement therapy may be effective in treating GHD, fatigue, and depression post ABI.

There is level 1b evidence that progesterone treatment improves long-term outcome and functionality, but results may not be observed short-term in ABI populations.

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