9. Neuroendocrine Disorders Post ABI

On behalf of the ERABI Research Group

9.1 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 the pituitary gland due to trauma was often not diagnosed until the post-mortem examination (Yuan & Wade 1991). Research indicates that neuroendocrine disorders vary in frequency 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%; recently, the rate has been quoted between 20 and 70% (Makulski et al. 2008; Sirois 2009).

Q. What does the research tell us about the pooled prevalence of hypopituitarism post brain injury?

Answer

- The pooled prevalence of hypopituitarism post TBI was 27% (Schneider et al. 2007).
- Neuroendocrine abnormalities, hypopituitarism and growth hormone deficiencies are common amongst those who sustain a TBI, especially those who sustain moderate to severe injuries (Popovic et al. 2005).

9.2 Anatomy of the Neuroendocrine System

Post-traumatic neuroendocrine disorders involving the pituitary gland can be divided into posterior or anterior pituitary dysfunction (APD) depending on which anatomical area is involved.

Anatomy of the Pituitary Gland

The pituitary gland consists of two lobes derived from two different embryological pouches:

- Anterior lobe (or adenohypophysis)
- Posterior lobe (or neurohypophysis)

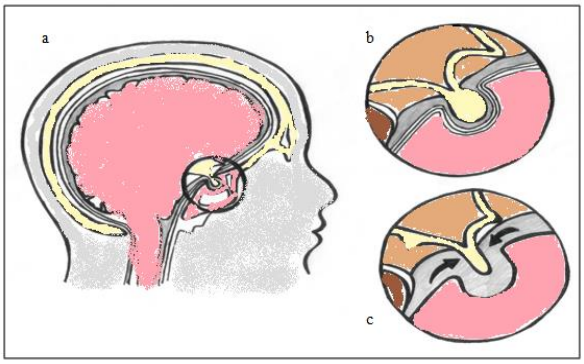


Figure 1. The pituitary gland under normal conditions (a and b), and how a traumatic injury effects its shape (c).

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). The six hormones produced include:

- Adrenocorticotropic hormone (ACTH)
- Growth hormone (GH)
- Thyroid stimulating hormone (TSH)
- Luteinizing hormone (LH)
- Follicle stimulating hormone (FSH)
- Prolactin (PRL)

These hormones serve to regulate endocrine systems in other areas of the body and are under the control of hypothalamic releasing factors.

Hypothalamic releasing factors correspond with the hormones released by the anterior pituitary. Their names and functions are summarized below (Table 1).

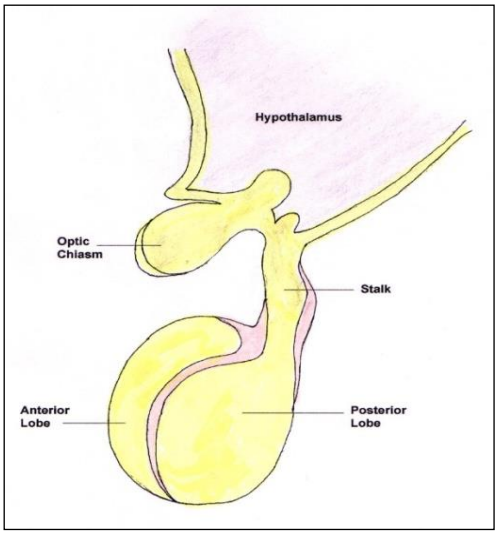


Figure 2. Diagram of the Hypothalamic-Pituitary Axis

Table 1. Hypothalamic Releasing Factors and the Bodily Response

Hypothalamic Releasing Factors	Action
Growth Hormone Releasing Hormone	Growth Hormone ↑
Somatostatin	Growth Hormone ↓
Thyrotropin Releasing Hormone	Thyroid Stimulating Hormone ↑
Luteinizing Hormone Releasing Hormone + Gonadotropin Releasing Hormone	Follicle Stimulating Hormone and Luteinizing Hormone ↑
Corticotropin Releasing Hormone	Adrenocorticotropic Hormone ↑
Prolactin Releasing Factor + Thyrotropin Releasing Hormone	Prolactin ↑

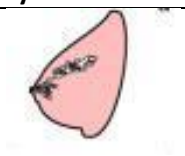
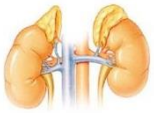
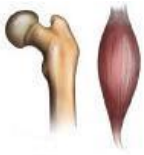
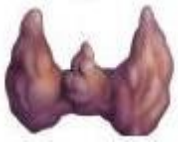
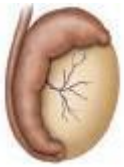
The posterior lobe contains the axons and nerve terminals of neurons which have their cell bodies in the hypothalamus. It is responsible for the secretion and storage of two hormones:

- Vasopressin or antidiuretic hormone (ADH) promotes water retention in the kidneys, which allows for concentration of urine.
- Oxytocin allows for milk let-down in the breast and causes uterine contractions during labour.

Hormones Involved with the Neuroendocrine System

The following table (Table 2) lists hormones released by either the anterior or the posterior pituitary glands and describes the accompanying bodily response of those hormones.

Table 2. Neuroendocrine Hormones Released and the Bodily Response

Glands	Hormones	Part of Body Affected		Body Response
Anterior Pituitary	PRL	Milk producing cells in the breast		Lactation, inhibition of GnRH, LH, FSH and gonadal hormones
	ACTH	Adrenal gland		Cortisol release from the adrenal cortex
	GH	Body cells		Growth
	TSH	Thyroid		T_3 and T_4 release from the thyroid leading to stimulation of growth and metabolism
	FSH	Testes		Androgen production (male sex hormones) and sperm production, testosterone secretion
	LH	Ovaries		Egg production, estrogen and progesterone secretion
Posterior Pituitary	ADH	Kidney		Increased water resorption at the level of the kidney leading to concentrated urine, water regulation
	Oxytocin	Uterus, breast		Uterine contractions during labour, milk let down reflex in the breast

PRL=Prolactin; ACTH=Adrenocorticotropic hormone; GH=Growth hormone; TSH=Thyroid stimulation hormone; FSH=Follicle stimulating hormone; LH=Luteinizing hormone; ADH=Antidiuretic hormone; GnRH= Gonadotropin-ReleasingHormone

9.3 Pathophysiology of Hypopituitarism Post ABI

Vascular Blood Supply of the Pituitary Gland

Early investigations of the pituitary gland have shown that the majority of the gland's blood supply comes from the long hypophyseal vessels (Stanfield 1960). The inferior hypophyseal artery supplies blood to the entire neurohypophysis and to a small section of the adenohypophysis (Behan et al. 2008; Sirois 2009).

Table 3. Vascular Supply of the Pituitary (Sirois 2009)

Anterior Pituitary	Posterior Lobe
a) Superior hypophyseal artery - Branch of internal carotid	a) Supply by inferior hypophyseal artery
b) Capillary plexus formation with portal vessels - Primary and secondary - Run down in the stalk with two long portal vessels	b) Short portal vessels
c) 90% of the anterior lobe is nourished by the portal system	c) 1 capillary plexus

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. This may be the direct result of trauma (skull fracture) or edema, hemorrhage, raised 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).

Injuries Associated with TBI

Table 4. Potential 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	
	Increase intracranial pressure	
	Hemorrhage	
	Inflammatory mediators	

Table 5. Types 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 abnormalities with neuroimaging abnormalities. The gold standard for neuroendocrine dysfunction is serum tests assessing hormonal function (Benvenga et al. 2000).

Isolated and Combined Hormone Deficiencies

Although early hormonal abnormalities are not necessarily associated with long-term post-traumatic hypopituitarism (PTHP; Klose et al. 2007), the most common problem following TBI is a single axis hormonal insufficiency.

Q. What does the research tell us about chronic hormone deficits in those who have sustained an ABI?

Answer

- 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. 2004; Bondanelli et al. 2004; Kelly et al. 2000; Lieberman et al. 2001).
- Abnormalities of antidiuretic hormone represent one of the most common endocrine disturbances in patients with TBI (Powner et al. 2006), along with adrenal insufficiency and diabetes insipidus (Bernard et al. 2006).

Clinical Presentation of Hypopituitarism

Q. How does hypopituitarism present clinically?

Answer

- Temperature lability
- Appetite disturbance
- Disorder of fluid regulation/hypertension
- Fatigue and/or 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 (Sesmilo et al. 2007; Sirois 2009)

Neuroendocrine disorders post TBI result from specific injuries to those areas of the brain that regulate physiological functions, 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.

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 have a much better prognosis than those who do not recover (Aimaretti et al. 2004; Bondanelli et al. 2004; Ghigo et al. 2005). In one study, 5.5% of patients who showed no signs of PTHP at 3 months did so later 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).

Q. What are some of the complexities or issues in the diagnosis of hypopituitarism post ABI?

Answer

- Post-traumatic hypopituitarism consists of non-specific features that can mimic other signs and symptoms commonly seen following TBI. There may be a delay in the presentation of post-traumatic hypopituitarism following injury and as a result, the diagnosis may be easily missed following ABI (Schneider et al. 2007).
- Some key indicators of post-traumatic hypopituitarism, such as serum-like growth factor, may already be low in older patients as a result of normal aging.
- Studies to date have failed to demonstrate a clear association between TBI severity, as measured by Glasgow Coma Scale or electroencephalogram, and the likelihood of developing hypopituitarism (Sirois 2009).

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. Although it has been shown by several researchers that PTHP patients had significantly lower GCS than unaffected survivors (Klose et al. 2007; Sirois 2009); this 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 hypopituitarism post TBI is primarily a disorder seen much more often with 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).

9.4 Neuroendocrine Laboratory Testing

Diagnosis

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; however, there is some dispute in the literature as to how soon after injury it should be considered, how often it should be conducted and who should be tested. As mentioned previously, clinical assessment of hypopituitarism is difficult because the signs and symptoms are often non-specific and mimic the neuropsychological sequelae of TBI. It is therefore reasonable to consider performing baseline hormonal evaluation in patients with more severe injuries. Early post injury, the most important anterior hormones to screen are TSH, GH and ACTH as these will lead more quickly to symptoms that may affect recovery; although, baseline testing of *all* hormones is still recommended as it allows for improved ease of clinical follow-up.

Screening for Hypopituitarism Post ABI

Q. Who should be tested for hormonal disorders or deficiencies?

Answer

- Current research suggests that patients with moderate to severe brain injury (GCS score 3–12) should undergo hormonal evaluation (Behan et al. 2008).
- Some discretion needs to take place in those patients with the most severe disability (e.g. vegetative state; Sesmilo et al. 2007).
- Individuals at greatest risk for post-traumatic hypopituitarism are those who have sustained a diffuse axonal injury and/or basal skull fracture, experienced diffuse cerebral swelling, hypotensive or hypoxic episodes, or who were older at the time of injury (Schneider et al. 2007).
- Length of stay in intensive care unit (i.e. longer duration of intubation), longer hospitalization and a prolonged loss of consciousness may also play a role (Klose et al. 2007).

Because hypopituitarism can evolve over time post injury, it is important to begin screening as soon as possible. In the acute stage, due to its life threatening potential, screening for adrenal insufficiency is important (Bernard et al. 2006). During this stage of recovery, cortisol levels of <7.2 µg/dL may indicate adrenal insufficiency. Treatment should also be considered and initiated in cases where hyponatremia, hypotension and hypoglycemia are present and cortisol levels are between 7.2 and 18 µg/dL (Schneider et al. 2007). For those who have had extended stays in the intensive care unit, increased intracranial pressure, diffuse axonal injury (DAI), or basal skull fractures assessing pituitary function may be necessary and should be considered. While 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. 2007); however, during the post recovery stage, at 3 and 6 months, a complete clinical assessment for hypopituitarism should be completed (Powner & Boccalandro 2008; Powner et al. 2006; Schneider et al. 2006). This is especially important if any of the following are noted: loss of secondary hair, impaired sexual function, weight changes, polydipsia, or amenorrhea.

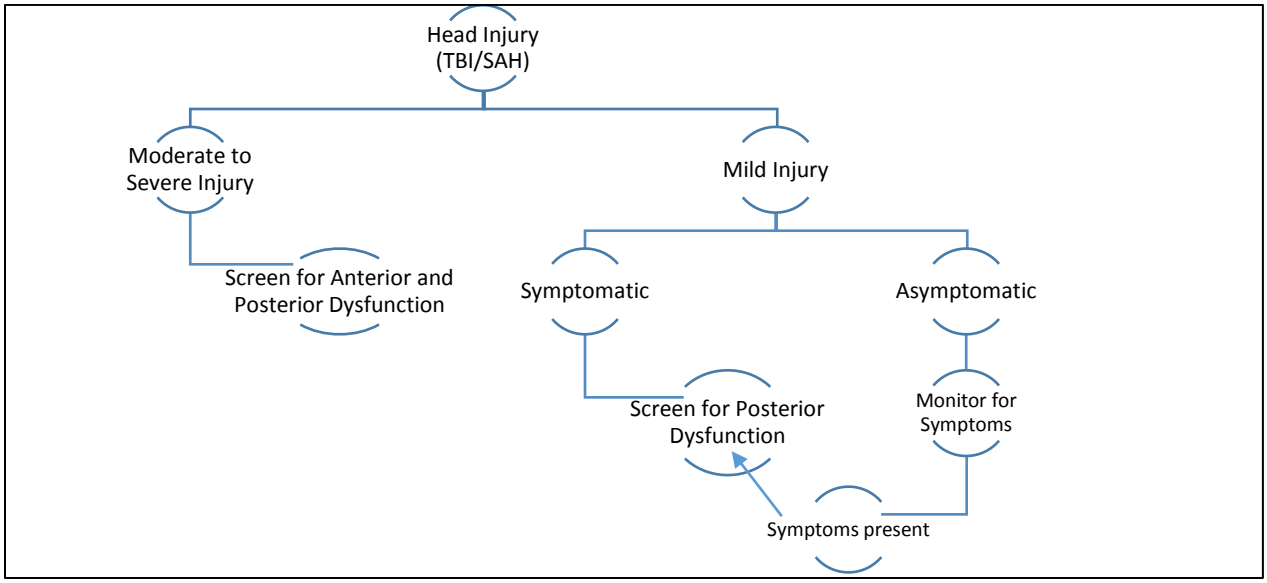


Figure 3. Screening for hypopituitarism based on severity of head injury (Estes & Urban 2005; Sirois 2009)

Q. What hormonal testing is recommended for all those who sustain an ABI?

Answer

Pituitary-Gonadal Axis

- Males: LH/FSH and testosterone are used to evaluate the pituitary gonadal axis function.
- Females: For those who have irregular cycles LH, FSH and estradiol need to be measured (Sesmilo et al. 2007).

Pituitary-Adrenal Axis

- The cut-off values used for diagnosing adrenal insufficiency are different in the acute phase following a TBI than in the rehabilitation phase. Pituitary-adrenal evaluations are best performed with early morning plasma cortisol measurements or a 24-hour urinary free cortisol test can also be used (Sesmilo et al. 2007).

Pituitary-Thyroid Axis

- Baseline testing should include thyroid function tests: TSH, fT_4, and fT_3 (Sesmilo et al. 2007).

Pituitary-Somatotropic Axis

- Insulin growth factor-1

Screening tests for disorders of fluid regulation

- Serum electrolytes
- Serum osmolarity
- Urine osmolarity

Hormonal screening should include 0900 AM serum cortisol, fT_3, fT_4, TSH, FSH, LH, testosterone in men and E_2 in women, PRL, and insulin growth factor 1 (IGF-1). In patients with polyuria or suspected DI, urine density, serum sodium and plasma osmolality should also be evaluated. Low IGF-I levels strongly predict severe GH deficiency (in the absence of malnutrition). Normal IGF-I levels may be found in patients with GH deficiency; therefore, provocative tests are necessary in patients with another identified pituitary hormone deficit. Provocative testing is recommended if IGF-I levels are below the 25^{th} percentile of age related normal limits (Ghigo et al. 2005).

Neuroimaging

Q. Which is the preferred neuroimaging technique to determine pituitary gland dysfunction and why?

Answer

- It has been found that magnetic resonance imaging is the preferred imaging technique for the pituitary gland as it can readily distinguish between the anterior and posterior lobes (Makulski et al. 2008).
- Magnetic resonance imaging allows for both visualization of structural abnormalities and indirect imaging of the blood supply.
- Most common pathological findings are hemorrhage of the hypothalamus and posterior lobe and infarction of the anterior lobe of the pituitary (Maiya et al. 2008; Makulski et al. 2008).
- While widely regarded as the best imaging technique, magnetic resonance imaging may still fail to show pathological abnormalities in some patients with post-traumatic hypopituitarism (Makulski et al. 2008).

Although neuroimaging—magnetic resonance imaging (MRI) or computed tomography (CT) scans—can be very successful in locating lesions within various sections of the brain, they are not entirely comprehensive. Benvenga et al. (2000) have found 6–7% of those with PTHP have no abnormalities on MRI; therefore further testing is necessary. With regards to diagnosis, blood tests remain the gold standard. Benvenga et al. (2000) suggest 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 of injury.

Provocative Testing

Growth Hormone Assessment

Q. What test can be done to rule out severe growth hormone deficiency?

Answer

- Approximately 20% of those with a TBI or subarachnoid hemorrhage are at risk for severe growth hormone deficiency. To rule this out provocative testing (e.g. insulin tolerance test and GHRH + arginine test) has been recommended.
- Due to the expense of provocative testing, it is only recommended when other hormonal tests, such as the insulin growth factor-1, have been completed and only to rule out other transitory hormone deficits (Sesmilo et al. 2007).

Insulin Growth Factor-1

It has been suggested that a relationship exists between IGF-1 and GHD; however, in a study conducted by Bondanelli et al. (2007) no relationship was found between IGF-1 and GHD as only 30% of patients with GHD were found to have low IGF-1 levels. This finding was supported by previous studies, indicating that low IGF-I does not necessarily predict GH status in those who have sustained an ABI (Bondanelli et al. 2005; Popovic et al. 2005).

Adrenocorticotropic Hormone Assessment

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).

Short Stimulation Test

In healthy subjects stimulated serum cortisol has been shown to be between 550 nmol/L and 1,110 nmol/L (19.6–39.6 lg/dL); thus a normal response is >550 nmol/L. Adrenocortical insufficiency is confirmed with a serum cortisol <500 nmol/L (18 lg/dL). Standard ACTH tests should be completed at the earliest 4 weeks post pituitary surgery (Auernhammer & Vlotides 2007).

Insulin-Induced Hypoglycemia Test

During an insulin-induced hypoglycemia test the top serum cortisol levels in healthy people are between 555 nmol/L to 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 in patients with epilepsy and cardiac complications for whom this test has been found to be contraindicated.

Metyrapone Test

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

Corticotropin-Releasing Hormone Test

Responses to this test vary widely among 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 6. Provocative Testing of Pituitary Function (Auernhammer & Vlotides 2007)

Tests	Methods
Growth hormone assessment	• IGF-1 is low • Assess family history: looking at age related issues and weight issues (obesity) 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 ‘‘overnight 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.
Corticotropin-releasing hormone (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.
Short ACTH stimulation test	250 µg recombinant human ACTH and serum cortisol, given intravenously. The responses are assessed at 0, 30 and 60 min.

9.5 Physiological Disorders

As mentioned earlier, TBI or ABI can result in significant hormonal abnormalities, which in turn can have a negative impact on physiological functioning. Consequences are generally the result of anterior and posterior pituitary dysfunction. The consequences of posterior pituitary dysfunction are shown below.

Posterior Pituitary Dysfunction

Antidiuretic Hormone Dysfunction

Q. What are the more common medical consequences of an acute TBI?

Answer

- Early studies investigating the impact of an ABI on the posterior pituitary gland have demonstrated a disruption in sodium and fluid balance (Doczi et al. 1982).
- The more common medical consequences of an acute TBI are disorders of salt and water balance resulting in syndrome of inappropriate secretion of antidiuretic hormone, hyponatremia and diabetes insipidus (Makulski et al. 2008).
- Abnormalities of antidiuretic hormone represent one of the most common endocrine disturbances that occur in patients following a TBI (Powner et al. 2006).

Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Syndrome of Inappropriate Secretion of ADH (SIADH) is characterized by sodium serum levels 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 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 done for those patients who had abnormal results at 3 and/or at 6 months. Assessment for SIADH 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, diuretics, vasopressin analogs, and chlorpromazine may lead to SIADH (Agha et al. 2005; Goh 2004; Haugen 2009).

Q. Following an ABI who is most likely to develop symptoms of syndrome of inappropriate secretion of antidiuretic hormone?

Answer

- Those who have sustained a severe ABI are more likely to develop symptoms of syndrome of inappropriate secretion of antidiuretic hormone than those with moderate or mild ABI.

Findings suggest that while SIADH post injury is not overly common, it has a greater incidence among patients with moderate/severe injuries (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 post injury, as was the case with one patient in the study by Kozlowski Moreau et al. (2012). Depending on the diagnostic criteria, SIADH is recognized as 'severe' if serum sodium is <130 mmol/L (Born et al. 1985) or <125 mmol/L (Doczi et al. 1982). Severe syndromes may be associated with poorer neurological function compared to "moderate" syndromes (i.e. serum sodium ≥130 mmol/L), and may require daily fluid restriction to resolve symptoms. There is not a widely accepted "target range" for fluid restriction. However, Doczi et al. (1982) suggest limiting daily fluid intake to less than 600 to 800 mL, whereas Born et al. (1985) suggest limiting intake to 250 to 500 mL.

Hyponatremia

Hyponatremia, defined as serum sodium concentration <136 mmol/L (Moro et al. 2007; Zhang et al. 2008), may result from SIADH or cerebral salt wasting (CSW; Moro et al. 2007).

Q. What are the symptoms of hyponatremia post ABI and its recommended treatment?

Answer

- Symptoms of hyponatremia include lethargy, coma, and/or seizures.
- Recommendations for the treatment of hyponatremia, resulting from syndrome of inappropriate secretion of antidiuretic hormone, include thyroid-releasing hormone stimulation and limiting daily fluid intake.

Q. What is the evidence relating to the efficacy of treatments available for the management of hyponatremia post ABI?

Answer

- There is Level 4 evidence that thyroid-releasing hormone may be effective in treating post ABI hyponatremia by reducing circulating antidiuretic hormone.
- There is Level 4 evidence that sodium supplementation therapy and hydrocortisone may be effective in treating post ABI hyponatremia.

Hyponatremia is undesirable from a recovery standpoint as it is associated with longer administration days and worse outcomes at 1 month from treatment (e.g. limited "good" recovery, higher number of patients with moderate disability; Moro et al. 2007). It is thus imperative that patients with post-injury hyponatremia receive treatments with demonstrated efficacy and safety. Recommendations for the management of hyponatremia resulting from SIADH include TRH stimulation (Zhang et al. 2008) and limiting daily fluid intake. The stimulation works by indirectly decreasing the level of circulating ADH in the blood, which allows the body to counteract the inappropriate elevation of ADH. The effectiveness of TRH stimulation, however, is limited against hyponatremia resulting from CSW (Zhang et al. 2008).

Other ways to manage post-injury hyponatremia include intravenous (IV) or oral Na^+ supplementation. Higher dosages of Na^+ may be necessary if hyponatremia persists (Moro et al. 2007). Hydrocortisone should be considered if Na^+ supplementation is ineffective. 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 (Moro et al. 2007).

Diabetes Insipidus

DI has been found to occur in patients with mild to severe TBIs and may last anywhere from a few days to a month post injury (Tsagarakis et al. 2005). Simply put, DI results results in a large amount of diluted urine being produced. Post-traumatic DI may result from swelling around the hypothalamus or posterior pituitary but as the swelling begins to resolve itself so does the DI (Agha et al. 2005). Individuals suffering from DI may experience severe thirst, polyuria and polydipsia (Blumenfeld 2002).

Q. Following a head injury, what has diabetes insipidus been linked to?

Answer

- Results suggest that diabetes insipidus may be linked to poor functional outcomes.

In their retrospective study, Hadjizacharia et al. (2008) reported that patients with DI had a significantly higher incidence of medical complications (jaundice, cardiac dysfunction, etc) than those without (33% vs. 19%; p=0.016). Patients in the DI group were also found to have a higher mortality rate

(Hadjizacharia et al. 2008). Having a DI may also predict deficiencies in other pituitary axes, such as hypogonadism (Schneider et al. 2008).

Q. What is the evidence relating to the occurrence of diabetes insipidus and the risk factors leading to its development?

Answer

- There is Level 4 evidence that the occurrence of diabetes insipidus ranges from approximately 2% to 15% post ABI.
- There is Level 4 evidence that extensive fractures at the base of the skull may serve as a risk factor for the development of diabetes insipidus post ABI.

Hadjizacharia et al. (2008), in a study of 436 patients with blunt or penetrating head injury, found 15.4% (n=67) developed DI. Onset of DI for most patients occurred within the first few days of admission to acute care (mean=1.2 days), with treatment beginning on average of 1.6 days post diagnosis. There was a significantly higher incidence of complications in the DI group when compared to the remaining group (p=0.016). Those at greatest risk for developing DI were those with a GCS score ≤8. Those in the DI group were also found to have a higher mortality rate. In studies with smaller samples, the rates ranged from approximately 2% (Bondanelli et al. 2007; Born et al. 1985; Ghigo et al. 2005) to 14% (Bondanelli et al. 2004). There are also suggestions that extensive fractures at the base of the skull may also be an important risk factor for DI (Born et al. 1985).

Q. What evidence is there supporting the administration of insulin growth factor 1 post ABI to improve clinical outcomes in those patients who have diagnosed with diabetes insipidus?

Answer

- There is Level 2 evidence suggesting that insulin growth factor-1 given post ABI may improve clinical outcomes in patients diagnosed with diabetes insipidus.

In a randomized controlled trial, Hatton et al. (1997) randomized patients with severe injuries (i.e. GCS 5–7) to the placebo or the treatment group, which received 5 mg IV IGF-I for 14 days. Both the control and treatment group were provided with nutritional support. In total five patients died during the study: two from the treatment group and three from the control group. Of those treated with IGF-I (n=11), eight improved from “poor” to “good” in Glasgow Outcome Scale (GOS) scores, whereas only three had made similar improvements from the placebo group. The finding suggests IGF-1 provide functional benefits in patients with post-ABI DI.

Anterior Pituitary Dysfunction

Early research indicated that damage to the anterior pituitary was likely to not be reported post ABI (Yuan & Wade 1991); however, APD is now increasingly recognized (Sandel et al. 2007). Damage to the APD may lead to a compromise in GH, thyroid, glucocorticoid (cortisol), sex hormone (testosterone in

men/estrogen in women), and PRL production (Sandel et al. 2007). Clinical presentation of APD varies widely, depending on the particular neuroendocrine axes affected, and 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).

Q. Following a TBI what does the research say about who is at greater risk for developing hormonal deficiency?

Answer

- Those with greater diffuse axonal injury or basal skull fracture.

A number of studies have identified risk factors for APDs following injury. In particular, Schneider et al. (2008) suggest that greater DAI, and basal skull fracture are associated with a higher risk of pituitary impairment. Despite that Schneider et al. (2008) found that age was associated with a higher risk of pituitary impairment, other authors have found no such relationship (Rosario et al. 2013; Moreau et al. 2012; Agha et al. 2004; Klose et al. 2007). Rosario et al. (2013) did report that admission FIM was associated with pituitary dysfunction. Findings from Klose et al. (2007) and Bondanelli et al. (2004) suggest that more severe injury may also play a predictive role in post-injury hypopituitarism. In contrast, Tanriverdi et al. (2007) and Agha et al. (2004) did not find differences in pituitary dysfunction by injury severity. Klose et al. (2007) reported that female gender and high body mass index were risk factors for pituitary dysfunction.

Growth Hormone Deficiency

Although GH deficiency is not uncommon following an ABI, it is not as quickly diagnosed as other hormone deficiencies (Lieberman et al. 2001). Often GH deficiency escapes detection for months or years post injury. Symptoms of GH deficiency 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 (Sandel et al. 2007; Schneider et al. 2007).

Q. What is the clinical presentation of growth hormone deficiency post ABI?

Answer

- Sleep disturbances.
- Energy loss, fatigue, attention/concentration disorders, decreased self-esteem, poor quality of life, headaches, decrease in cognitive performance, depression, irritability, insomnia.
- Muscle wasting, decrease lean body mass, weight gain (visceral obesity), dyslipidemia, osteoporosis.
- Decreased maximal oxygen consumption, atherosclerosis, hypertension, fatigability, decrease in exercise tolerance.

The prevalence of post-injury GH deficiency varies considerably across studies, ranging from 2.8–63.6% (Agha et al. 2005; 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; Kozlowski Moreau et al. 2012; Lieberman et al. 2001; Schneider et al. 2006; Tanriverdi et al. 2007). Persistent deficiencies up to and beyond 12 months were commonly noted (Agha et al. 2005; 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).

Multiple findings suggest that higher BMI is associated with higher incidence of post-injury GH deficiency (Agha et al. 2004; Lieberman et al. 2001; Schneider et al. 2006). Other predictors of GH deficiency include low IGF-1 levels (Agha et al. 2005; Agha et al. 2004; Bondanelli et al. 2007; Lieberman et al. 2001; Olivecrona et al. 2013; Schneider et al. 2006), older age (Bondanelli et al. 2004; Schneider et al. 2006), and more severe injury (Kleindienst et al. 2009). Conversely, Agha et al. (2005), Aimaretti et al. (2005), and Bondanelli et al. (2004) did not find that GH deficiency was associated with BMI. Similarly, Agha et al. (2005) and Bondanelli et al. (2004) did not find that GH deficiency was associated with injury severity.

Outcomes associated with GH deficiency are not well documented, but findings do suggest that cognitive functions (Bondanelli et al. 2007; Kozlowski Moreau et al. 2012), performance on FIM (Bondanelli et al. 2007; Rosario et al. 2013), and results in DRS (Bondanelli et al. 2004) are negatively impacted by the presence of GH deficiency. Olivecrona et al. (2013) reported no significant relationship between GH or IGF-1 levels and GCS or GOS. Tanriverdi et al. (2007) supports this finding in that they found no significance difference in GH levels or outcome (non-surviving vs. surviving) by injury severity groups.

Gonadotropin Deficiency/Luteinizing Hormone + Follicle Stimulating Hormone Deficiency

Hypogonadism is often one of the earliest symptoms of hypopituitarism in those who survive a TBI (Lee et al. 1994). For 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. Low levels of estradiol in the absence of elevated FSH may 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. 2007). Testosterone deficiencies in males and estradiol deficiencies in women may also be a sign of hypogonadism.

Q. How does gonadotropin deficiency present itself?

Answer

- Hypogonadism leading to oligomenorrhea, amenorrhea, infertility, sexual dysfunction, decreased libido/muscle atrophy, osteoporosis, loss of hair
- ↓ tolerance to exercise
- ↓ memory and cognitive performance
- Muscle atrophy, osteoporosis, loss of hair

Note: Despite knowing how gonadotropin deficiency presents, there is very little evidence suggesting possible treatments post ABI.

Gonadotropic deficiency is common among individuals with ABI, whereby acute prevalence rates range from 13–80% (Agha & Thompson 2005; Aimaretti et al. 2005; 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; Kozlowski Moreau et al. 2012; Lieberman et al. 2001; Schneider et al. 2006).

Common predictors of post-injury GD include older age (Agha et al. 2004), transient DI, polytrauma, hypoxia (Schneider et al. 2008), 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); however, 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 lower FIM gains per day (Rosario et al. 2013), total FIM score, level of Cognitive Functioning Scale scores, and Disability Rating Scale scores (Bondanelli et al. 2007), poorer Glasgow Outcome Scale scores (Agha & Thompson 2005), and less clinical improvement on the modified Rankin Scale (Schneider et al. 2006). However, one study (Tanriverdi et al. 2007) reported that the rate of GD did not differ between individuals who survived and did not survive.

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. Of note, all patients with hyperprolactinemia also had an infection, were hypoglycemic, or were on dopamine antagonists, GABA agonists, opiates or central catecholamine depletors. All of these medications are known to increase PRL levels.

Findings outlined above suggest that rate of post-ABI hyperprolactinemia vary across studies. For instance while Kopczak et al. (2014) in their large population study reported that 17.3% (88 of 509) showed elevated levels of PRL post injury, Agha et al. (2005) reported that more than 50% (26 of 50) of patients had developed hyperprolactinemia acutely following injury. It is important to note, however, that the rate of post-injury hyperprolactinemia may be smaller if the number of patients receiving hyperprolactinemia-inducing drugs is excluded from the analysis (Kopczak et al. 2014; Lieberman et al. 2001; Schneider et al. 2006). Therefore, the rate of hyperprolactinemia directly attributable to ABI may be lower than that currently reported.

Post-injury hyperprolactinemia may persist up to 12 months post injury (Agha et al. 2005; Ghigo et al. 2005; Kleindienst et al. 2009; Schneider et al. 2006), however, given the apparent lack of association with negative outcomes (Agha et al. 2005; Olivecrona et al. 2013), hyperprolactinemia may not be a significant deterrent to patient recovery.

It is difficult to predict whether individuals sustaining ABI will develop hyperprolactinemia, as indicated by Agha et al. (2004), who reported that post-injury hyperprolactinemia was not associated with factors

such as age, GCS score, cerebral edema, or operative mass evacuation. However, a later study did report that GCS scores were negatively correlated to post-injury PRL levels, suggesting more severe injuries (low GCS score) may predict higher PRL levels (Tanriverdi et al. 2007).

Adrenocorticotropic Hormone Deficiency

The ACTH secretion tends to fluctuate at night and increase with stress, physical activity and chronic disease. The symptoms of ACTH can include weakness, nausea, fever and shock, weight loss, hypotension, hypoglycemia, hyponatremia, myopathy, anaemia, eosinophilia and limited energy output (Schneider et al. 2007). Cortisol levels taken in the morning are low and there is a poor cortisol response to ACTH stimulation (Sandel et al. 2007).

Q. How does adrenocorticotropic hormone deficiency present clinically?

Answer

- Fatigue, weakness, anorexia, nausea, vomiting
- Decrease hair
- Low blood pressure
- Hypoglycemia, poor quality of life
- Absence of hyperpigmentation (only present in primary deficiency)

Findings from multiple studies suggest that ACTH (or cortisol) deficiency immediately following an ABI (i.e. within 1 week of injury) can vary considerably in rate, ranging from 8.8% (9 of 102; Tanriverdi et al. 2007) to 70.5% (31 of 44; Olivecrona et al. 2013).

It is suggested that the severity of injury 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). Other factors may include older age, injury to the basal skull, lack of cranial vault fracture (Schneider et al. 2008), and the initial GCS score (Tanriverdi et al. 2007). It is important to note, however, that there are inconsistencies with regards to whether these aforementioned factors do in fact play a role in inciting post-injury corticotropic complications (Agha et al. 2005; Agha et al. 2004; Bondanelli et al. 2007; Olivecrona et al. 2013), thus some caution is necessary when interpreting the findings.

Individuals living with ABI may continue to demonstrate post-injury ACTH deficiency for up to 12 months (Ghigo et al. 2005) and even beyond (Kleindienst et al. 2009). This may be problematic from the recovery standpoint, as post-injury ACTH deficiency has been shown to be associated with poorer cognitive and physical outcomes (Kozlowski 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). Compounding the problem is the lack of known treatment options available to manage post-injury ACTH deficiencies.

Thyroid Stimulating Hormone Deficiency

TSH deficiency appears to be less common than other hormonal deficiencies post ABI (Schneider et al. 2007). A decrease in thyroid function may lead to a decrease in an individual's basal metabolic rate, cognitive function, memory and an increase in levels of fatigue (Elovic 2003). In children, TSH deficiencies may lead to growth delays (Alexopoulou et al. 2004). Individuals may also present with bradycardia, hypotension, myopathy, neuropathy, changes to the skin, hair and voice, and myxedema; however many of these symptoms do not present themselves until much later in an individual's recovery period (Schneider et al. 2007).

Q. What is the clinical presentation of thyroid stimulating hormone deficiency?

Answer

- Fatigue
- Anemia
- Paleness
- Cold intolerance
- Muscle atrophy/cramps
- Weight gain, depression
- Loss of outer 1/3 of eyebrow, coarse hair
- Coarse voice, macroglossia
- Pre-orbital edema
- Bradycardia
- Constipation
- Neuropsychiatric disorders (hallucinations, delirium)

Multiple studies found that post-ABI thyrotropic deficiency is uncommon, with very few (i.e. 1–5) individuals displaying symptoms at or greater than 6 months post injury (Agha et al. 2005; Agha et al. 2004; Bondanelli et al. 2007; Kelly et al. 2000; Klose et al. 2007). It is suggested that severe injuries as well as prolonged ventilation (>24 hours) are associated with impaired thyrotropic functions (Kleindienst et al. 2009). Such deficiencies are undesirable from a recovery standpoint since they confer not only poor physical outcomes but also poor cognitive outcomes (Kozlowski Moreau et al. 2012).

9.6 Treatment

Q. What does the literature tell us about the appropriate time to begin treatment post ABI?

Answer

- To date there is no relevant data or guidelines on when to treat, how to treat or what medication(s) 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 resulting from a motor vehicle accident may be at even greater risk, regardless of the severity of injury, due to the rotational forces which the brain is subjected to (Estes & Urban 2005).
- It is reasonable to repeat screening at a minimum 6 and 12 months post injury and again at 18 and 24 months post injury in those who had a severe injury or early diabetes insipidus.

Conditions that require immediate treatment are ACTH, ADH, TSH and pan-hypopituitarism. GH deficiency has been shown to improve with time and may improve as other deficiencies improve; therefore, it is not necessary to begin treatment the moment it is diagnosed, particularly if it is an isolated incidence. Also treatment in the acute phase is not recommended for GH deficiency as there appears to be no benefit (Sirois 2009). For those who sustain a mild TBI and a GH deficiency has been noted during regular blood work, but no other symptoms have appeared, it is suggested waiting 3 years post trauma to begin treatment to see if the condition will reverse itself. If possible, when there is clear indication of anterior or posterior pituitary dysfunction consulting an endocrinologist is strongly recommended (Estes & Urban 2005).

Q. What is the recommended treatment for adrenocorticotropic hormone deficiency?

Answer

- Hydrocortisone: 20 mg in morning and 10 mg early evening; the medication can be given orally, intramuscularly, or intravenously
- Prednisolone: 5 to 7.5 mg per day (to be given orally 1×/day)

Immediate Hormone Replacement Therapy

Q. What medication has been recommended in the treatment of hormone replacement therapy?

Answer

- Somatropin: 0.06 mg/kg subcutaneous or intramuscular (3×/week) has been recommended as a treatment for hormone replacement therapy.

Immediate hormone replacement therapy should be administered to patients with confirmed isolated or severe gonadal insufficiency.

Gonadal Steroid Therapy

Androgen Replacement in Men or Testosterone Therapy

Q. What is the recommended treatment for hypogonadism in males post ABI?

Answer

- Testosterone therapy is recommended for males who are diagnosed with hypogonadism post ABI.
- Testosterone therapy can be administered in a variety of ways: implants, oral test therapy, intramuscular therapy, transdermal patches, intramuscular injection.

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

Estrogen Replacement in Women

Hormone replacement therapy in women has been shown to be effective in women during their menopausal or perimenopausal years; however, long term treatment is not recommended due to the negative benefit-risk ratio (Auernhammer & Vlotides 2007). Treatment for women may include the administration of dehydroepiandrosterone (most abundant circulating steroid hormone in humans) daily or testosterone and although some success has been found using these treatments, neither has been approved.

Growth Hormone Replacement Therapy

Q. What is recommended when there is a confirmed growth hormone deficiency?

Answer

- Synthetic growth hormone (or growth hormone-releasing hormone): given by injection subcutaneously (either through a syringe or pen). The maximum dose recommended is 0.06 mg/kg and is given subcutaneously or intramuscularly 3×/week.

In patients where there has been a confirmed GH deficiency, the introduction of GH replacement therapy has been recommended (Auernhammer & Vlotides 2007). The goal of therapy is to elevate serum IGF-I levels to the mid to high range. This range will vary depending on age and gender. GH is

generally administered subcutaneously. Although this treatment has been tested with individuals who have not sustained a brain injury, there is no literature looking at this treatment within the ABI population.

Replacement Therapy for Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Q. What medication is given to treat syndrome of inappropriate antidiuretic hormone secretion?

Answer

- Conivaptan: generally given intravenously (20 mg/day) for short periods of time.

Treatments for hyponatremia include fluid restriction and administration of hypertonic saline solution. These treatments may be administered alone or with loop diuretics (Arai et al. 2009). Conivaptan is a new medication that has been approved for use by the US-Food and Drugs Administration to treat hypervolemic hyponatremia, but again it has yet to be studied within the ABI population.

Treatment of Diabetes Insipidus

Q. What medication has been recommended to treat diabetes insipidus?

Answer

- Desmopressin: 0.1–0.4 mL/day intranasally.

DI has been found to be a leading cause of death in those who sustain a severe TBI (Maggiore et al. 2009). Desmopressin has been shown to reduce urine output and liquid intake (Alaca et al. 2002).

Secondary Adrenal Insufficiency

Q. What medication has been recommended to treat secondary adrenal insufficiency?

Answer

- Hydrocortisone: 20 mg in the morning and 10 mg early evening; medication can be given orally, intramuscularly, or intravenously.

Moro and colleagues found that the administration of hydrocortisone was beneficial in reducing the amount of sodium excretion in a small group of patients with a TBI (Moro et al. 2007). Although the risk of adverse effects appears to be low, when administering hydrocortisone, more research is needed.

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