

Educational Module 9

Neuroendocrine Disorders Post Acquired Brain Injury

9. Neuroendocrine Disorders Post Acquired Brain Injury

9.1 History and Epidemiology

Neuroendocrine disorders, primarily hypopituitarism, was first diagnosed by the German researcher Cyran in 1918¹⁻³. Until recently damage to the hypothalamus and pituitary gland following trauma was often not diagnosed until the post mortem examination¹⁷. Recent research indicates neuroendocrine disorders vary post traumatic brain injury (TBI)¹⁸ and what was once thought to be a rare occurrence is now increasingly diagnosed^{1;19;20}. In the early 1950's, the incidence of hypopituitarism post injury was thought to be 1%; however, the rate has recently been quoted between 20 and 70%^{3;14}.

Q1. What does the research tell us about the pooled prevalence of hypopituitarism post stroke and ABI?

Answer

1. The pooled prevalence of hypopituitarism post TBI was 27% and post stroke it was 47%.
2. Neuroendocrine abnormalities, hypopituitarism and growth hormone deficiencies are common amongst those who sustain a TBI, especially those who sustain a moderate to severe TBI.

Figure 9.1 Pituitary Gland: Normal Condition and Post Traumatic Condition

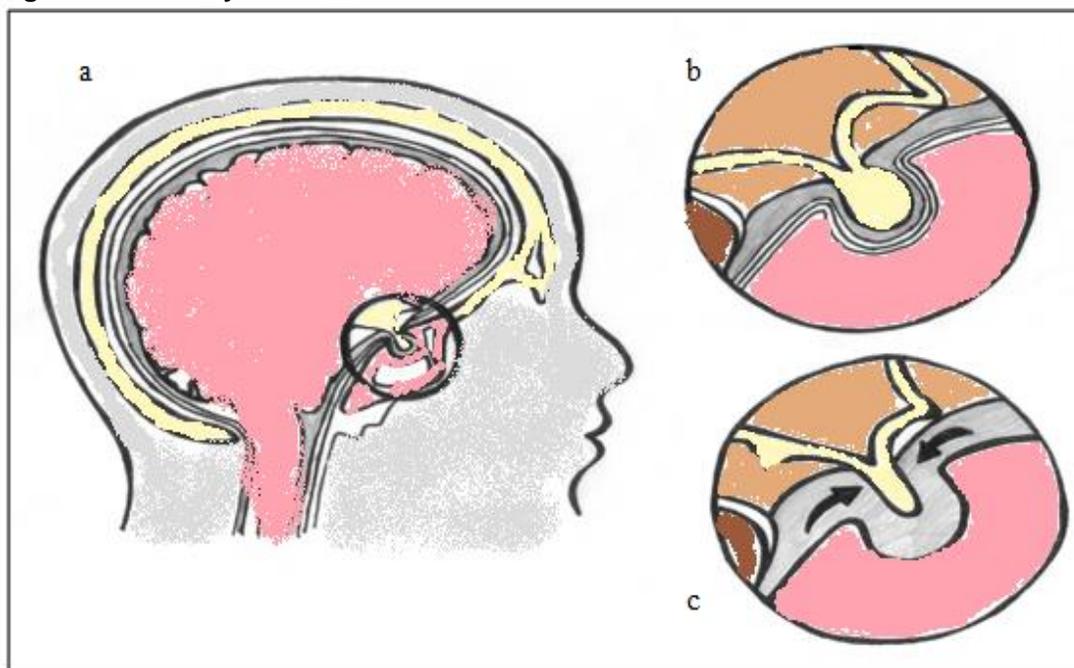


Figure 9.1 shows the pituitary gland under normal conditions (9.1a and 9.1b) and how it can suffer injury during and following a traumatic injury (9.1c).

9.2 Anatomy of the Neuroendocrine System

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

9.2.1 Anatomy of the Pituitary Gland

The pituitary gland consists of two lobes derived from 2 different embryological pouches.

- Anterior lobe (or adenohypophysis)
- 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 **posterior lobe** contains the axons and nerve terminals of neurons which have their cell bodies in the hypothalamus.

The **anterior lobe** is responsible for the production of six important hormones which are secreted into the circulatory system²⁵. The six hormones produced include:

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

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

Hypothalamic releasing factors correspond with the hormones released by the anterior pituitary and include:

- Growth hormone releasing hormone → growth hormone release
- Somatostatin → decreases release of growth hormone
- Thyrotropic releasing hormone → thyroid hormone release
- LHRH/GnRH → FSH and LH release
- Corticotrophic releasing hormone → ACTH release
- Prolactin releasing factor (PRF) and throtropin-releasing hormone (TRH) → prolactin

The **posterior lobe** is responsible for the secretion and storage of 2 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.

9.2.2 Hormones Involved with the Neuroendocrine System

Following an ABI/TBI changes may be noted in hormones released by the pituitary gland²⁶. Hormones released include:

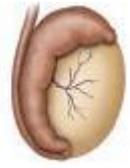
Table 9.1 Hormones Produced and Released by the Pituitary Gland

Glands	Hormones
Anterior pituitary	<ul style="list-style-type: none"> • ACTH (AdrenoCorticotropic Hormone or Corticotropin) • TSH (Thyroid-Stimulating Hormone or Thyrotropin) • PRL (Prolactin or Luteotropic hormone (LTH)) • GH (Growth Hormone) • FSH (Follicle-Stimulating Hormone) • LH (Luteinizing Hormone)
Posterior pituitary	<ul style="list-style-type: none"> • Oxytocin • ADH (AntiDiuretic Hormone or Vasopressin)
Hypothalamo-pituitary	Gonadotropins: <ul style="list-style-type: none"> • LH (Luteinizing Hormone) • FSH (Follicle Stimulating Hormone) • HCG (Human Chorionic Gonadotropin)
Gonads Glands (Ovaries or Testes)	<ul style="list-style-type: none"> • Testosterone • Estradiol • Antimullerian Hormone • Progesterone • Inhibin B and Activin

The following table (Table 9.2) lists those hormones that are released by both the anterior or posterior pituitary glands and the body's response to this.

Table 9.2 Hormone Released and the Body's Response

Glands	Hormones	Part of Body Affected		Body Response
Anterior Pituitary	Prolactin	milk producing cells in breast		lactation
	Adrenocorticotrophic Hormone (ACTH)	adrenal gland		adrenalin
	Growth Hormone (GH) (Somatotropin)	body cells		growth

				
	Thyroid Stimulating Hormone (TSH)	thyroid		stimulation of growth and metabolism
	Follicle- Stimulating Hormone (FSH)	testes		androgen production (male sex hormones) and sperm production. testosterone secretion
	Luteinizing Hormone (LH)	ovaries		egg production, estrogen and progesterone secretion
Posterior Pituitary	Antidiuretic Hormone (ADH)	kidney		regulation of water levels
	Oxytocin	uterus		labour contractions

9.3 Pathophysiology of Hypopituitarism Post ABI

9.3.1 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 vessels²⁴ The inferior hypophyseal artery supplies blood to the entire neurohypophysis and to a small section of the adenohypophysis^{9;14}.

Table 9.3 Vascular Supply of the Pituitary¹⁴

Anterior Pituitary

- a) Superior hypophyseal artery
- Branch of internal carotid

- b) Capillary plexus formation with portal vessels
 - Primary and secondary
 - Run down in the stalk with 2 long portal vessels
- c) 90 % of the anterior lobe is nourished by the portal system

Posterior Lobe

- a) Supply by inferior hypophyseal artery
- b) Short portal vessels
- c) 1 capillary plexus

9.3.2 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 result of direct trauma (skull fracture) or oedema, haemorrhage, 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 often occurs as the result of inflammation and edema around the posterior pituitary gland; however, this has been shown to improve with time ⁹.

9.3.3 Injuries Associated with TBI

Potential lesions associated with traumatic brain injury are shown in Table 9.4. The types of injuries are listed below in Table 9.4.

Table 9.4 Potential Hypothalamic-Pituitary-Adrenal (HPA) lesions associated with Traumatic Brain Injury ¹⁴

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

Table 9.5 Types of Injury ²³

Type of Injury	Percentage
Haemorrhage of hypothalamus	29%
Haemorrhage 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 is serum testing tests assessing hormonal function ²³.

9.3.4 Isolated & Combined Hormone Deficiencies

Although early hormonal abnormalities are not necessarily associated with long-term PTHP ¹³, the most common problem following TBI is a single axis or hormonal insufficiency.

Q2. What does the research tell us about chronic hormone deficits in those who have sustained an ABI.

Answer

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^{2;5-7}.

1. Among individuals with an ABI growth hormone deficiencies may be seen in 20% of those injured; gonadal hormone deficiencies in another 15%-30%, prolactin elevation in 30% and hypothyroidism in 10%–30% of the population.
2. Chronic adrenal insufficiency and diabetes insipidus (DI) post ABI occurs much more commonly, especially in those with a severe TBI ^{10;12}.

Table 9.6 Isolated and Multiple Pituitary Axes Affected (%)

Post traumatic phase	1 axis (single deficiency)	2 or more (multiple deficiencies)
Acute	48%	28%
3 months	6.5%	6.5%
12 months	4.3%	6.5%

9.3.5 Clinical Presentation of Hypopituitarism

Neuroendocrine dysfunction may be seen as temperature lability, disturbances in appetite, weight fluctuations, hypothalamic and pituitary disorders, disorders of fluid regulation, hypertension or hypotension, fatigue, increased anxiety, depression, memory failure, cognitive deficiencies, reduced bone and muscle mass and immunologic disorders ^{8;14}.

Q3. How does hypopituitarism present clinically?

Answer

1. Fatigue,
2. Sleep Disturbance,
3. Decreased muscle mass, increased fat mass,
4. Reduced exercise tolerance and muscle strength,

5. Amenorrhea, decreased libido, erectile dysfunction,
6. Decreased cognitive function, concentration, memory,
7. Mood disturbances, depression, irritability,
8. Social isolation, decreased quality of life.

Neuroendocrine disorders post TBI result from specific injuries to those areas that regulate physiological functions in various regions of the brain, specifically injuries along the hypothalamic-pituitary axis¹⁸. Symptoms will vary depending on the area of the brain that has been affected by the injury.

Q4. Who does the current research suggest be tested for hormonal disorders or deficiencies?

Answer

1. Current research suggests that anyone who suffers a brain injury (whether the result of a stroke or a traumatic brain injury) and has a GCS between 3 and 12 should be tested for hormonal disorders or deficiencies⁹.
2. Some discretion needs to take place in those patients with the most severe disability (vegetative state)⁸.
3. 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.
4. Length of stay in ICU, longer hospitalization and a prolonged loss of consciousness may also play a role in the development of hypopituitarism¹³.

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^{6,7,21}. In one study, 5.5% of patients who showed no signs of PTHP deficiencies 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 months²¹. Growth hormone deficiency has been shown to be the most common deficit^{7,21}.

Q5. What are some of the complexities or issues in diagnosis hypopituitarism post ABI.

Answer

1. Due to the nature of its features and the delay of its presentation, hypopituitarism may be missed following a stroke or an ABI⁴.
2. Some of the key indicators, such as low serum-like growth factor, may already be low in older patients due to normal aging.

3. Studies looking at this issue to date indicate TBI severity, as measured by the GCS or EEGs, is not an accurate indicator of the likelihood of developing hypopituitarism.
4. There is however, a trend to show an association with TBI severity¹⁴.

9.3.6 Association with Severity of ABI

There is as of yet no clear association of the development of PTHP with the severity of TBI, 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^{13;14;19}; this has not been a consistent finding^{19;21}. 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 function²².

Benvenga et al.²³ have noted that hypopituitarism post TBI is primarily a disorder seen much more often with male survivors between the ages of 11 and 39 years. This is likely related to the fact that greater number of younger males tend to sustain head injuries more often. Currently there is no evidence that specific types of head injuries are more likely to lead to hypopituitarism²⁰. Due to the life threatening consequences associated with pituitary dysfunction, it represents a negative prognostic factor²³.

9.4 Neuroendocrine Laboratory Testing

9.4.1 Diagnosis

Q6. What hormonal testing is recommended for all those who sustain an ABI?

Answer

Pituitary-Gonadal Axis

1. Male Patients: LH, FSH and testosterone are used to evaluate the pituitary gonadal axis.
2. Female Patients: for those who have irregular cycles LH, FSH, and estradiol needs to be measured⁸.

Pituitary-Adrenal Axis

1. The cut off values used for diagnosing adrenal insufficiency is 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 24 hour urinary free cortisol test can also be used⁸.

Pituitary-Thyroid Axis

1. It has been suggested, baseline testing should include thyroid function tests (TSH, fT4, fT3) and repetition of testing where appropriate⁸.

Discussion

Diagnosis is based on clinical evaluation, laboratory testing and neuroimaging. According to Sesmilo et al.⁸ baseline hormonal testing should be performed in all patients; however, there is some dispute in the literature as to when it should be completed (how soon after injury), how often and who should be tested. As mentioned previously, clinical assessment of hypopituitarism is difficult because the signs and symptoms are often nonspecific and often mimic the neuropsychological sequelae of TBI. It is therefore reasonable to consider performing baseline hormonal evaluation in more severe TBI or SAH patients. Early post injury the most important anterior hormones to screen may be thyroid, growth and Adrenocorticoid axes as these will lead more quickly to symptoms that may affect recovery although baseline testing of all hormones allow more easy clinical follow-up.

9.4.2 Screening for Hypopituitarism Post ABI

Q7. What are the guidelines for screening patients who have sustained an ABI?

Answer

1. Hypopituitarism is a common and treatable condition resulting from an ABI.
2. Guidelines for screening patients who have sustained an ABI or a stroke include:
 - a) severity of injury, location of injury (those with basal skull fractures, diffuse axonal injury, or increased intracranial pressure),
 - b) GSC (especially those who score between 3 and 12), length of time spent in the intensive care unit (ICU)
 - c) and the amount of time that has passed since the injury occurred¹⁵.

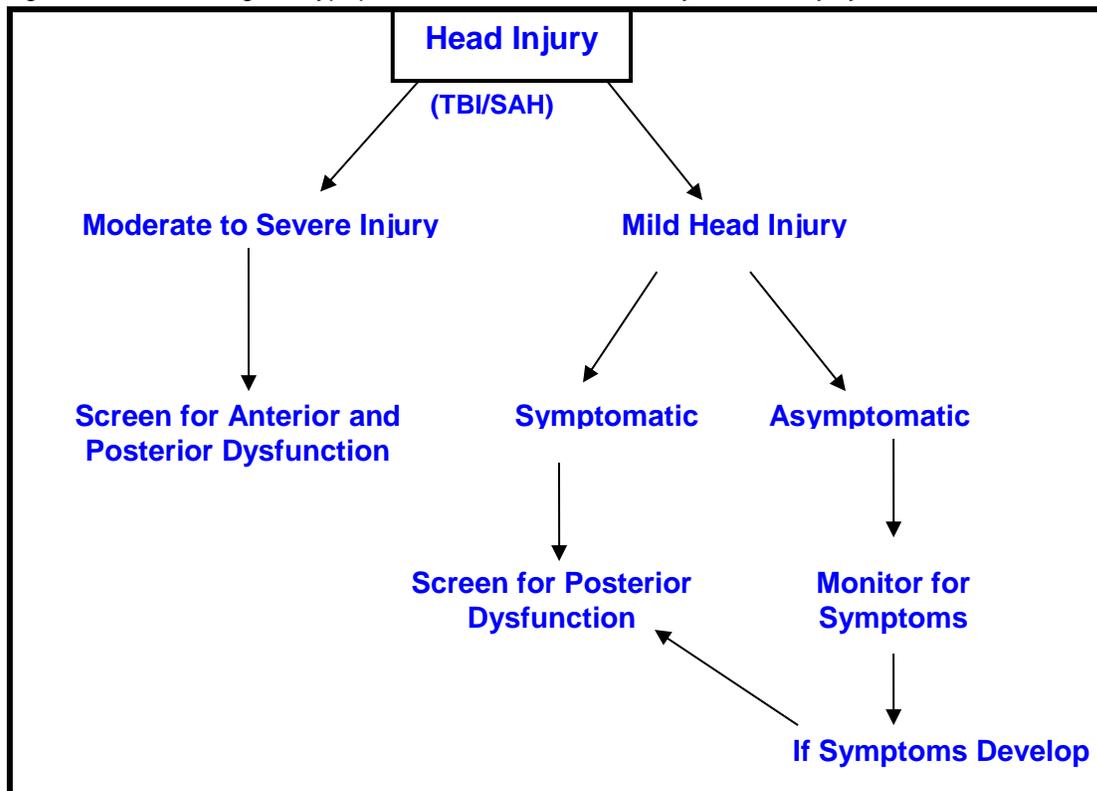
Discussion

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 important¹². During this stage of recovery, cortisol levels of less than 7.2ug/dL may indicate adrenal insufficiency. Treatment should also be considered and initiated in those cases where hyponatremia, hypotension and hypoglycaemia are present and cortisol levels are between 7.2 and 18ug/dL¹⁵. For those who have extended stays in the ICU and increased intracranial pressure, diffuse axonal injury, 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 supplementation of these hormones during this phase is beneficial^{15;20}; however, during the post recovery stage, at 3 and 6 months, a clinical assessment for hypopituitarism should be completed^{10;27;28}. This is especially important if any of the following are noted: loss of secondary hair, impaired sexual function, weight changes, polydipsia, or amenorrhea.

For mild TBI it has been suggested to test only patients who spend more than 24 hours in hospital, who have an abnormal CT scan, or who initially have symptoms suggesting post-traumatic hypopituitarism.

Hormonal screening should include 0900 AM serum cortisol, fT3, fT4, TSH, FSH, LH, testosterone in men and E2 in women, prolactin, and IGF-I. In patients with polyuria or suspected diabetes insipidus, urine density, sodium and plasma osmolality should also be evaluated. Low IGF-I levels strongly predict severe growth hormone deficiency (in the absence of malnutrition). Normal IGF-I levels may be found in patients with growth hormone 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 25th percentile of age related normal limits²⁰.

Figure 9.3 Screening for hypopituitarism based on severity of head injury^{14;16}



9.4.4 Neuroimaging

Q8. Which is the preferred neuroimaging technique to determine pituitary gland dysfunction?

Answer

1. It has been found that magnetic resonance imaging (MRI) is the preferred imaging technique for the pituitary gland as it can readily distinguish between the anterior and posterior lobes³.

2. An MRI allows for both visualization of structural abnormalities and indirect imaging of the blood supply.
3. The most common pathological findings are haemorrhage of the hypothalamus and posterior lobe and infarction of the anterior lobe of the pituitary^{3;11}.
4. While widely regarded as the best imaging technique, MRI may still fail to show pathological abnormalities in some patients with post traumatic hypopituitarism³.

Discussion

Although neuroimaging (MRI or CT scans) can be very successful in locating lesions within various sections of the brain, they do not reveal all. Benvenga et al.²³ have found 6 to 7% of those with post traumatic hypopituitarism have no abnormalities on MRI; therefore further testing is necessary. **With regards to testing, blood tests remain for the gold standard.** Benvenga et al.²³ 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.

9.4.5 Provocative Testing

Growth Hormone Assessment

Q9. What test can be done to rule out severe growth hormone deficiency?

Answer

1. It has been noted that approximately 20% of those with a TBI or SAH are at risk for severe growth hormone deficiency; therefore, to rule this out **provocative testing** has been recommended.
2. Due to the expense of this test, it is recommended when other hormonal tests, such as the IGF-I, have been completed and only to rule out other transitory hormone deficits⁸.

Insulin Growth Factor (IGF)-1

It has been suggested that a relationship exists between IGF-1 and growth hormone deficiency; however, in a study conducted by Bondanelli et al.²² 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^{19;26}.

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 to 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 ²⁹.

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); 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 done 4 weeks at the earliest after pituitary surgery ²⁹.

Insulin-Induced Hypoglycemia Test

During an insulin-induced hypoglycaemia 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) ²⁹. Adrenocortical insufficiency is diagnosed when there is a serum cortisol increase of <500nmol/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 contra-indicated.

Metyrapone

Metyrapone has been shown to block the last step in the biochemical pathway from cholesterol to 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 to 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” require other diagnostic cut-offs of serum 11-deoxycortisol levels. In order to sustain this multi-step testing patients must be hospitalized. Metyrapone may cause gastrointestinal upset and may lead to adrenal insufficiency ²⁹. Currently this test is considered only if other tests are inconclusive.

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 ²⁹.

Table 9.7 Tests of Pituitary Function ²⁹

Tests	Methods
Growth hormone assessment	<ul style="list-style-type: none"> • 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 (<40 mg/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	30 mg/kg orally at midnight with a snack to minimize gastrointestinal discomfort. Blood for serum 11b-deoxycortisol,

test'	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, traumatic or acquired brain injury can result in significant hormonal abnormalities which in turn can have a negative impact on physiological functioning. Consequences are generally a result of anterior and posterior pituitary dysfunction. The consequences of pituitary dysfunction are shown below.

Table 9.8 Hormone Delivery and the Effects of Insufficiency (p.326³)

Pituitary				
Anterior pituitary				
Somatotrophs	Lactotrophs	Gonadotrophs	Thyrotrophs	Corticotrophs
~50% of cells growth hormone (GH)	~10%-25 % of cells prolactin (PRL)	~10%-15% of cells lutenizing hormone (LH) and follicle stimulating hormone (FSH)	~3%-5% of cells thyroid stimulating hormone (TSH)	~15%-20% of cells adrenocorticotrophic hormone (ACTH)
Targets				
Musculoskeletal System	Mammary gland	Gonads and Ovaries	Thyroid gland	Adrenal gland
Symptoms of Insufficiency				
↑ abdominal fat LDL ↓ muscle mass, vigor, concentratio HDL	↑ lactation secretion of estrogen and progesterone	↑ facial wrinkles ↓ libido fertility, pubic hair & axillary hair	↑ dry skin, weight, depression, fatigue & cognitive deficits ↓ cold tolerance & heart rate	↑ depression, anxiety, fatigue, apathy, nausea, vomiting, & under stress, hypoglycemia hyponatremia ↓ weight, strength & skin color
Posterior Pituitary				
Oxytocin		Vasopressin		
Targets				
Mammary gland and Uterus		Kidney and Arterioles		
Symptoms of Insufficiency				
↑ lactation & uterine contractions		↑ blood pressure & water retention		

9.5.1 Posterior Pituitary Dysfunction

9.5.1.1 Antidiuretic Hormone Dysfunction (ADH)

Q10. What are the more common medical consequences of an acute TBI?

Answer

1. Early studies investigating the impact of an ABI on the posterior pituitary gland have demonstrated a disruption in sodium and fluid balance.
2. The more common medical consequences of an acute TBI are disorders of salt and water balance resulting in inappropriate secretions of antidiuretic hormone (SIADH), hyponatremia and diabetes insipidus (DI).
3. Abnormalities of antidiuretic hormone represent one of the most common endocrine disturbances that occur in patients following a TBI ¹⁰

9.5.1.2 Syndrome of Inappropriate Secretion of ADH (SIADH)

Q11. Following an ABI who is most likely to develop symptoms of SIADH?

Answer

1. Those who have sustained a severe ABI were more likely to develop symptoms of SIADH. Researchers suggest restricting fluid intake to assist in the resolution of symptoms

Discussion

SIADH has been diagnosed in patients when sodium serum levels drop below 135mEq/L (hyponatremia) ³⁰ coupled with an inappropriate elevation of urine osmolality ²⁵. Given that adrenal insufficiency can be life-threatening, it should be evaluated when suspected in the acute phase ⁸. 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 3-6 months. Assessment for growth hormone deficiency should not be performed until other hormonal deficiencies have been managed ⁸. It has been suggested that the use of medications such as carbamazepine, SSRI, diuretics, vasopressin analogs, and chlorpromazine may lead to SIADH ³⁰⁻³².

In a review of 1808 ABI patients conducted by Doczi et al. ³³, the authors reported 84 patients developed SIADH, with the majority of these patients suffering a moderate (n=60) to severe (n=19) head injury. Of the 84 patients, 43 were found to have developed severe SIADH. Patients' were diagnosed with elevated intracranial pressure resulting from suspected brain edema, and each required strict fluid restriction. In this group of patients, serum sodium levels were found to be below 125 mmol/litre and each had an osmolality below 270 mosm/kg. Deterioration of the original injury and the development of complications can result in a delay in the diagnosis of SIADH.

In another study, conducted by Born et al.³⁴, of the 36 patients who were diagnosed with a severe ABI, all developed signs of SIADH. Six were diagnosed within 4 days of injury (early syndrome), while in the remaining patients SIADH became noticeable 7 or more days (late syndrome) post injury. The authors also noted that 33% of patients who underwent surgery showed signs of SIADH. Authors suggested limiting fluid intake (250 to 500 ml per 24 hours) to resolve symptoms.

9.5.1.3 Hyponatremia

Q12. What are the symptoms of hyponatremia post ABI and its recommended treatment?

Answer

1. Symptoms of hyponatremia include lethargy, coma, or seizures.
2. Recommendations for the treatment of hyponatremia, resulting from SIADH, include limiting daily fluid intake.
3. Administering saline or oral salt appears to be an effective treatment for hyponatremia post ABI.
4. The death rate for those diagnosed with hyponatremia is 60% higher than for patients who do not have it.

Discussion

Hyponatremia, defined as serum sodium concentration less than 136 mmol/L³⁵ may result from SIADH or cerebral salt wasting. Prevalence rates for severe hyponatremia among the ABI population have been found to range from 2.3% to 36.6%³⁶.

Zhang et al.³⁷, looked at the development of central hyponatremia in a group of ABI patients (n=68; GCS scores were 3-15) and a group of non-ABI patients (n=24). Blood osmotic pressure was only found to be significantly different between those with a mild or moderate ABI compared to those with a severe TBI. Test results showed urine osmotic pressure was significantly different (p<0.01) between the ABI group and the non-ABI group. No significant differences were noted within the 3 ABI groups. Blood sodium levels between the ABI group and the non-ABI group were found to be significantly different with the ABI group having lower sodium (Na⁺) concentrations in their blood than the non-ABI group (p<0.02). Within the ABI group, the majority of patients (n=25) who had sustained a severe TBI were diagnosed with hyponatremia and were found to have a significantly lower Na⁺ than those in the mild to moderate ABI groups (p<0.05)³⁷.

Moro et al.³⁸ conducted a review of 298 patient files and found 50 patients presented with signs of hyponatremia. Those diagnosed with hyponatremia were found to have worse outcomes, longer stays in hospital and most were diagnosed within the first 3 days of injury. Treatment included sodium supplementation therapy, which was effective for 37 patients. The remaining 13 patients received sodium supplementation therapy and sodium retention therapy with hydrocortisone. The administration of the hydrocortisone

allowed the serum sodium levels to reach the normal range within 3 days as sodium excretion was reduced as was urine volume.

Zafonte and Mann³⁹ and Chang et al.³⁶ each published case studies where hyponatremia was present. Zafonte and Mann⁴⁰ noted that the patient's sodium level had decreased to 120mEq/dL, she had lost weight and was clinically dehydrated. The patient was treated intravenously with normal saline and oral salt supplementation. An improvement was found in the patient's serum sodium levels within days.

Chang et al.³⁶, in a case study reported on a patient who experienced a rapid drop in his serum sodium levels. This coupled with the results of his other blood tests indicated the presence of hyponatremia. Treatment for this patient included the administration of hypertonic saline and fluid restriction. Over time and after 3 more episodes of hyponatremia, sodium levels increased and stabilized.

9.5.1.4 Diabetes Insipidus (DI)

Q13. Following a severe head injury, what has diabetes insipidus been linked to?

Answer

1. Results of several studies indicate that DI has been linked to lower GCS, lower GOS and a higher mortality rate.

Discussion

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 injury⁴¹. Simply put, DI results “*in the production of large amounts of diluted urine*”. Post traumatic DI may result from swelling around the hypothalamus or posterior pituitary but as the swelling begins to resolve itself so does the DI⁴². Individuals suffering from DI may experience severe thirst, polyuria and polydipsia²⁵.

Hadjizacharia et al.⁴³, in a study of 436 head injured patients, found 15.4% (n=67) developed diabetes insipidus. Onset of diabetes insipidus 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 whose GCS was ≤ 8 . Those in the DI group were also found to have a higher mortality rate.

Agha et al.⁴⁴ found 13 out of 50 ABI patients developed DI within the first 11 days post injury. It was also noted that these patients had a lower GCS score than those who did not develop DI. Diabetes insipidus was treated with desmopressin, subcutaneously at first and then orally. Six months post injury only 4 of the 13 patients were found to have persistent DI. At the 12 month, 3 patients were still being treated for DI. When accessing patient outcomes, using the GOS, 5 of the 13 with DI had Glasgow Outcome scores between 1 and 3.

Q14. What evidence is there supporting the administration of IGF-I post ABI to improve clinical outcomes in those patients who have diagnosed with DI?

Answer

1. There is Level 2 evidence suggesting IGF-I given post ABI may improve clinical outcomes in patients diagnosed with DI.

Discussion

In an RCT, Hatton et al. ⁴⁵ randomized patients with GCS 5-7 initially to placebo or to the treatment group that received insulin-like growth factor-I (IGH-I) administered as 5 mg rhIGF-I/1ml citrate/NaCL, pH6 via a continuous intravenous infusion within the first 72 hours that continued for 14 days. Both the control and treatment group were provided with nutritional support. In total 5 patients died during the study: 2 were in the treatment group and 3 were in the control group. Study results indicate those in the treatment group gained weight even though they had a lower caloric intake and higher energy expenditure. The control group lost weight and were found to have greater nitrogen outputs and daily glucose concentrations. Nitrogen intake during week 2 was significantly less in the treatment group ($p=0.002$) when compared to the control group. Nitrogen output was greater in the control group over the two week study period, compared to the treatment group. Glucose concentrations were also higher in the control group, when compared to the treatment group during the study period. GOS improved, from poor to good, for 8 of the remaining 11 patients in the treatment group. In the control group, the Glasgow Outcome Scale improved in only 3 patients.

9.5.2 Anterior Pituitary Dysfunction

Q15. Following a TBI what does the research say about who is at greater risk for developing a hormonal deficiency?

Answer

1. Those who suffer from moderate to severe TBIs are at greater risk for developing hormonal deficiencies.
2. This may lead to a poorer outcome following a TBI as hypopituitarism has been shown to negatively influence recovery.

Discussion

Early research indicated that damage to the anterior pituitary dysfunction (APD) was likely to not be reported post ABI ¹⁷; however, APD is now increasingly recognized ¹⁸. Damage to the APD may lead to a compromise in growth hormone (GH), thyroid, glucocorticoid, sex hormone (testosterone in men/estrogen in women), and prolactin production ¹⁸. 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 collapse¹⁸.

Bondanelli et al.²² noted that anterior hypopituitarism occurred in 26% of the TBI patients in their study. All were approximately, 6 months to one-year post injury. These results compared well to previous studies which noted anterior hypopituitarism occurred in about one-third of those who were 5 years post injury^{21;46}. Results also indicated that the LH-FSH and GH axes were directly related to the high occurrence of isolated deficiencies²². Furthermore, complete hypopituitarism was detected in only 1.4% of the 72 participants in the study. Study authors also found that pituitary dysfunction did not appear to be related to the GCS which was noted in several previous studies.

In a systematic review, Urban et al.⁴⁷ concluded that regardless of the severity of injury, APH deficiencies (including GH deficiency) in those who had had a TBI were more common than originally thought. Difficulties in diagnosis arise because these hormonal deficiencies can produce physical and psychological symptoms which mimic symptoms generally associated with other brain trauma pathology. Urban et al.⁴⁷ noted that the consequences of these hormonal abnormalities can be significant; for instance, hypopituitarism can increase the risk of ischemic heart disease and even a shortened life span.

Schneider et al.^{28;48} found that 56% of the 78 TBI patients who participated, had a least one pituitary axis impairment. Overall, no significant differences were noted when looking at GCS, modified Rankin scores, BMI, and age between those with and without hypopituitarism. Those with impaired GH secretion were found to be older and had higher BMIs, and lower IGF-I levels. Twelve months post injury fewer patients were affected, but several new cases were diagnosed.

Tanriverdi et al.^{49;50} in a study of 53 individuals diagnosed with a TBI, measured hormonal levels during the acute stage of recovery and one year post recovery. During the acute stage of recovery, several patients were found to have at least one hormonal deficiency (hyperprolactinemia (n=6) and low T₃ syndrome (n=27)). A comparison of mean hormone levels from the acute phase to the post recovery period of 12 months revealed no significant differences in the following levels: fT₄, PRL, LH, free testosterone and ACTH. When looking at total testosterone levels, TSH, fT₃, FSH and IGF-I increased significantly (p<0.05), while GH levels and cortisol levels decreased over the 12 month period⁵⁰. Tests completed at 3 years post injury, revealed 7 of the original 13 diagnosed as GH deficient were fully recovered, with one patient being newly diagnosed. Of those diagnosed as ACTH deficient, 5 of the 6 had recovered and one more patient was newly diagnosed⁴⁹. Tanriverdi et al.⁴⁹ found that GH deficiency, the most common deficiency post ABI, improved over time in those with mild or moderate ABIs, but those with severe ABIs had persisting symptoms. Another study conducted by Tanriverdi et al.⁵¹, found that basal hormone levels (cortisol, prolactin and total testosterone (males only)) were related to severity of injury.

Agha et al.⁵² in one of the largest studies of individuals (n=102) with a moderate to severe TBI found a high prevalence of undiagnosed hypopituitarism. More than a quarter of study subjects were found to have a large amount of undiagnosed anterior hormone deficiency. Those who were GH-deficient had a significantly higher body mass index (p=0.003) and lower IGF-I concentrations (p<0.001) than GH-sufficient patients.

No relationship was found between the GCS, age and other pituitary hormone abnormalities and deficiencies of the GH or ACTH ($p > 0.05$)⁵².

Cernak et al.⁵³ found changes in hormonal levels were affected by the level of injury a patient had sustained. Those with severe injuries were diagnosed with greater hormonal changes. In patients with a mild TBI TSH levels were elevated for the first 3 days following an injury; however, in patients with a severe injury TSH levels remained low for the first 7 days following the injury. T₃ levels remained low in those with a severe TBI throughout the study; however, T₄ levels appeared to be unchanged in all groups regardless of the level of injury.

9.5.2.1 Growth Hormone Deficiency

Q16. What is the clinical presentation of growth hormone deficiency post ABI?

Answer

1. Sleep disturbances
2. Energy loss, fatigue, attention/concentration disorders, no self-esteem, poor quality of life, headaches, decrease in cognitive performance, depression, irritability, insomnia
3. Muscle wasting, decrease lean body mass, weight gain (visceral obesity), dyslipidemia, osteoporosis
4. Decrease VO₂max, atherosclerosis, HBP, fatigability, decrease in exercise tolerance.
5. Routine endocrine testing should be conducted on TBI patients throughout their recovery as deficiencies may impair recovery.

Discussion

Although growth hormone deficiency (GHD) is not uncommon following an ABI, it is not as quickly diagnosed as other hormone deficiencies². Often GHD escapes detection for months or year post injury. Symptoms of growth hormone 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^{15;18}.

Leiberman et al.² examined at the prevalence of neuroendocrine disorders in those who had sustained a TBI and noted that GHD was diagnosed in 7 of the 48 patients tested. To diagnose GHD deficiencies the authors used glucagon and L-dopa stimulation tests as the majority of patients were diagnosed with a severe TBI. Further testing (IGH-I testing) was also conducted confirming the presence of GHD in these 7 patients. Of the initial 70 patients who participated, early morning cortisol levels were lower in 46%. In 15 patients, blood work revealed TSH or FT₄ levels were below the normal range. Overall, 36 patients had a single abnormal axis, while 12 were diagnosed with two abnormalities. The remaining 22 patients were found to have no abnormalities². Given these abnormalities can impair recovery, the study authors recommended the routine testing of TBI patients.

9.5.2.2 Gonadotropine Deficiency/LH-FSH Deficiency

Q17. How does gonadotropine deficiency present itself?

Answer

1. Hypogonadism – oligomenorrhea, amenorrhea, infertility, sexual dysfunction, decreased libido\muscle atrophy, osteoporosis, loss of hair
2. Reduced tolerance to exercise
3. Decreased memory and cognitive performance
4. Despite the knowing how gonadotropine deficiency present, there is very little evidence suggesting possible treatments post ABI.

Discussion

Hypogonadism is often one of the earliest symptoms of hypopituitarism in those who survive a TBI⁵⁴. For males it is important to monitor testosterone concentrations as low levels in the absence of elevated luteinizing hormone (LH) levels may indicate hypogonadism. In premenopausal women monitoring estradiol levels is important. Low levels of estradiol in the absence of elevated follicle stimulating hormone (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^{15;55}. Testosterone deficiencies in males and estradiol deficiencies in women may also be a sign of hypogonadism.

There appears to be some uncertainty 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.⁵⁵, suggest testing TBI patients at least one year after injury for hypogonadism. Agha and Thompson⁵⁶ suggest testing 3 to 6 months post injury, with follow-up testing at 12 months.

Two studies have examined the development of hypogonadism post ABI. Kleindienst et al.⁵⁷ reported gonadotropic dysfunction was found in both genders. Deficiencies were noted in 13% of patients upon admission to hospital. Twenty more patients were diagnosed with a deficiency within the first week post injury. Study results also indicated that those who had sustained more severe injuries had either lower testosterone levels or luteinising hormone levels. In an earlier study, Lee et al.⁵⁴ found similar results. In their study of males who had sustained a TBI, all were found to have altered levels of testosterone post injury. Fourteen of the twenty-one participants had an abnormally low serum concentration of testosterone, while the remaining 7 had levels towards the lower end of the normal range.

9.5.2.3 Hyper/Hypoprolactinemia

Hyperprolactinemia has been shown to be present in more than half of ABI patients in the early acute phase and it is believed that symptoms may be present in 30% of patients diagnosed with hyperprolactinemia¹⁹. Kilimann et al.⁵⁸ found males had higher levels of prolactin than females and more males were found to have hyperprolactinemia

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

9.5.2.4 Adrenocorticotrophic Hormone Deficiency (ACTH)

Q18. How does ACTH deficiency present clinically?

Answer

1. Fatigue, weakness, anorexia, nausea, vomiting
2. Decrease hair
3. Low blood pressure
4. Hypoglycaemia
5. Absence of hyperpigmentation (only present in primary ACTH deficiency (Addison Disease))
6. Maybe life threatening if acute.

Discussion

The ACTH secretion tends to fluctuates 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 output¹⁵. Cortisol levels taken in the morning are low and there is a poor cortisol response to ACTH stimulation¹⁸.

9.5.2.5 Thyroid-Stimulating Hormone Deficiency (TSH)

Q19. What is the clinical presentation of TSH 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 oedema
- Bradycardia
- Constipations
- Neuropsychiatric disorders (hallucinations, delirium)

Discussion

Thyroid-stimulating hormone (TSH) deficiency appears to be less common than other hormonal deficiencies post ABI⁴. 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 fatigue⁵⁹. In children TSH deficiencies may lead to growth retardation⁶⁰. 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 period¹⁵.

Diagnosing TSH has been shown to be more difficult as the symptoms are often masked by other hormonal deficiencies post ABI. TSH is often treated with levothyroxine (1 mg orally before breakfast)⁶¹.

9.6 Treatment

Q20. What does the literature tell us about the appropriate time to begin treatment post ABI.

Answer

1. To date there is no relevant data or guidelines on when to treat, how to treat or what medication to administer.
2. It has been suggested that testing should begin immediately for those individuals who have been diagnosed with a moderate or severe ABI¹⁶, and are no longer in a coma or vegetative state.
3. Those who sustain diffuse axonal injuries (DAI) resulting from a MVA may be at even greater risk, regardless of the severity of injury, due to the rotational forces which the brain is subjected to¹⁶.
4. 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.

Q21. What is the recommended for the treatment of ACTH?

Answer

1. Hydrocortisone: 20 mg in morning and 10 mg early evening. The medication can be given orally, intramuscularly, or by IV.
2. Prednisolone: 5 to 7.5 mg per day (to be given orally and 1 x a day).

Discussion

Conditions that require immediate treatment are ACTH, ADH, TSH and panhypopituitarism. GHD as been shown to improve with time and may improve as other

deficiencies improve; therefore, it is not necessary to begin treatments the moment it is diagnosed particularly if it is an isolated incidence. Also treatment in the acute phase is not recommended for GHD as there appears to be no benefit ¹⁴. For those who sustain a mTBI 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** ¹⁶.

9.6.1 Immediate Hormone Replacement Therapy (HRT)

Q22. What medication has been recommended in the treatment of HRT?

Answer

1. Somatropin 0.06 mg/kg subcutaneous or intramuscular (3x/wk) has been recommended as a treatment for HRT.

Discussion

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

9.6.2 Gonadal Steroid Therapy

9.6.2.1 Androgen Replacement in Men or Testosterone Therapy

Although growth hormone deficiency (GHD) is not uncommon following an ABI, it is not as quickly diagnosed as other hormone deficiencies ². Often GHD escapes detection for months or year post injury. Symptoms of growth hormone 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 ^{15;18}.

Q23. What is the recommended treatment for hypogonadism in males post ABI?

Answer

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

Discussion

Treatments for hypogonadism include implants (implanting of 3 to 6 pellets of unmodified testosterone (200mg) subcutaneously every 4 to 6 months), oral testosterone

replacement therapy, intramuscular injections (of testosterone esters), transdermal patches, transdermal gels, and buccal delivery⁶². 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.

9.6.2.2 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 ratio²⁹. Treatment for women may include the administration of DHEA daily or testosterone and although some success has been found using these treatments, neither has been approved.

9.6.3 Growth Hormone Replacement Therapy

Q24. What is recommended when there is a confirmed growth hormone deficiency?

Answer

1. Synthetic GH (or GHRH) which is given by injection subcutaneously (either through a syringe or pen) is recommended. The maximum dose recommended is 0.06 mg/kg and is given subcutaneously or intramuscularly 3x/week.

Discussion

In patients where there has been a confirmed growth hormone deficiency (GHD), the introduction of growth hormone replacement therapy has been recommended²⁹. 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. Growth hormone 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.

9.6.4 Replacement Therapy for SIADH

Q25. What medication is given to treat SIADH?

Answer

1. Conivaptan which is generally given intravenously (20 mg/day) is often given for shorts periods of time.

Discussion

Treatments for hyponatremia include fluid restriction and administration of hypertonic saline solution. These treatments may be administered alone or with loop diuretics⁶³. Conivaptan, a new medication has been approved for use by the US-FDA to treat hypervolemic hyponatremia, but again it has yet to be studied within the ABI population.

9.6.5 Treatment of Diabetes Insipidus

Q26. What medication has been recommended to treat diabetes insipidus?

Answer

1. Desmopressin (DDAVP): 0.1 to 0.4 ml/day intranasally has been suggested to treat diabetes insipidus

Discussion

Diabetes insipidus has been found to be a leading cause of death in those who sustain a severe TBI⁶⁴. Desmopressin has been shown to reduce urine output and liquid intake⁶⁵.

9.6.6 Secondary Adrenal Insufficiency

Q27. What medication has been recommended to treat secondary adrenal insufficiency?

Answer

1. Hydrocortisone: 20 mg in the morning and 10 mg early evening. Medication can be given orally, intramuscularly, or by IV

Discussion

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 TBI³⁸. Although the risk of adverse effects appears to be low, when administering hydrocortisone, more research is needed.

Conclusions

Neuroendocrine dysfunction post ABI is more frequent than initially thought. The prevalence varies considerably among studies and this may reflect the inaccuracy of actual testing methods. Neuroendocrine disorders often result in a variety of symptoms such as: temperature lability, appetite disturbances, decreased muscle mass, sleep

disturbances, decreased hair, decreased libido, and disorders of fluid regulation, or hypertension¹⁴. With the exception of diabetes insipidus other neuroendocrine disorders remain under reported and under diagnosed. Testing should be done while the patient is in acute care for ACTH and ADH deficiencies and then during the next 12 months for the remaining hormones. Although TSH is not a frequent deficit in the TBI patient GH, ACTH and LH/FSH are. Failure to diagnose these dysfunctions could impact the individual's recovery process and impact their overall quality of life.

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