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Pituitary Pitfalls: Guidance for Physiatric Diagnosis and Management of Post-TBI Hypopituitarism

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Clinical Vignette

AP is a 20-year-old right-handed female with a history of polycystic ovarian syndrome who was hospitalized after being a pedestrian struck by motor vehicle. She sustained polytrauma including a severe traumatic brain injury manifested by bilateral temporal epidural hematomas and subarachnoid hemorrhage. She returned home approximately 3 months post-injury after completing a 6-week inpatient rehabilitation course.

Six months post-injury, she complained of ongoing lower extremity spasticity and reported facial acne with hair loss and new amenorrhea since her accident. She was enrolled in outpatient physical therapy but was recently experiencing more fatigue during her sessions with episodes of lightheadedness affecting her participation. She lost weight during her initial hospitalization, but her weight had since stabilized.

Physical exam was notable for facial rash affecting both cheeks with extension to the chin and upper neck as well as hair thinning. Her blood pressure was low normal without symptoms of orthostasis. Her left knee spasticity was graded Modified Ashworth Scale (MAS) of 1+ and she had 2-3 beats of bilateral ankle clonus.

She presented to the UPMC Physical Medicine and Rehabilitation Brain Injury Clinic to discuss her constellation of symptoms, which were impeding her quality of life.

Definition of the Problem

Traumatic brain injury (TBI) occurs when an external force is applied to the brain resulting in temporary or persistent brain dysfunction. It is a major cause of morbidity and mortality in the United States with over 64,000 TBI-related

deaths in 2020 and 223,000 TBI-related hospitalizations in 2019.[1] TBI can affect cognitive, functional, and psychosocial domains and contribute to medical complications with overlapping symptoms. Abnormalities in the hypothalamic-pituitary axis, termed post-traumatic hypopituitarism (PTHP), is one example that negatively impacts clinical outcomes.

While severity criteria remain a topic of active debate, TBI is commonly classified as mild, moderate, or severe. Studies support injury severity as a risk factor for PTHP; individuals with moderate to severe TBI are more likely to be affected.[2] The presence of diffuse axonal injury and basilar skull fractures has also been associated with increased prevalence of PTHP.[3]

Onset of neuroendocrine dysfunction may be acute (hours to days) or chronic (greater than 3 months) following TBI. The urgent and at times life threatening endocrine conditions (most commonly adrenocorticotropic and antidiuretic hormone deficiencies) are typically managed in the critical care setting to reduce morbidity and mortality. By contrast, most individuals with chronic PTHP present in the outpatient setting with vague symptoms that can make diagnosis more challenging.

Studies suggest that up to one third of individuals with TBI may have persistent anterior pituitary dysfunction.[4] One systematic review investigating hypopituitarism in the chronic phase after TBI and aneurysmal subarachnoid hemorrhage found the prevalence to be 27.5%[5] while another systematic review looking at all TBI severity classifications found that 31.6% had at least one anterior pituitary abnormality.[4] While most cases are reported in the moderate to severe TBI population, relationships between pituitary dysfunction and mild, specifically sports-related head injury, are becoming more apparent. A study of retired football players reporting lower quality of life found that 23.5% had hypopituitarism (6) and another study noted that 22.7% and 9.1% of amateur kickboxers showed deficiencies in growth hormone (GH) and adrenocorticotropic hormone (ACTH), respectively.[7]

In the outpatient setting, individuals with chronic PTHP may express non-specific complaints of fatigue, mood disturbance, or cognitive impairments. As these symptoms frequently overlap with post-concussive syndrome and other medical co-morbidities, PTHP can remain undiagnosed and untreated further limiting rehabilitation gains and reducing qualify of life. Table 1 summarizes common symptoms in individuals with pituitary hormone deficiencies.

Table 1: Common symptom manifestation of post-traumatic hypo-pituitarism related pituitary hormone dysfunction in the clinic setting

Pituitary Hormone	Symptoms that may be reported/ observed with dysfunction
Adrenocorticotropic Hormone	Fatigue, low blood pressure, weakness, weight loss, confusion
Gonadotropin (LH/FSH)	Fatigue, mood disturbances Male: lower libido, erectile dysfunction, decreased muscle mass Female: menstrual irregularities
Growth Hormone	Fatigue, cognitive impairments, mood disturbances, reduced exercise tolerance
Prolactin	Galactorrhea, otherwise similar as LH/FSH suppression
Thyroid Stimulating Hormone	Fatigue, weight gain, hair thinning, cold intolerance, neurophysiologic disturbances, cognitive impairments
Antidiuretic Hormone	Polyuria, polydipsia (more likely early after TBI; less likely in outpatient setting)
Oxytocin	No confirmed adverse effects related to deficiency

Presentation of Chronic Post-traumatic Hypopituitarism in the Outpatient Setting

An overview of normal pituitary gland anatomy and physiology is provided in Figure 1.

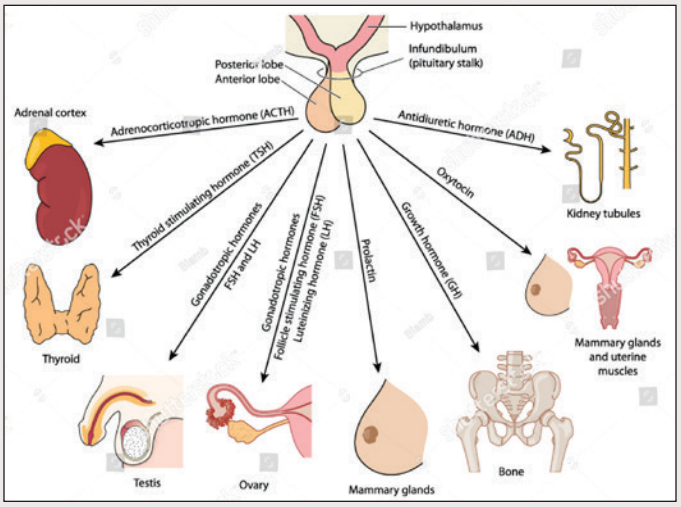

Figure 1: Normal Pituitary Gland Anatomy and Physiology

Adrenocorticotropic Hormone (ACTH)

ACTH stimulates the adrenal glands to produce androgens (secondary sexual characteristics), glucocorticoids (metabolism and immune responses), and mineralocorticoids (blood pressure, vascular volume, electrolyte regulation and stress response). When deficient, an acute stressor can lead to potentially life-threatening adrenal crises. Less critical manifestations include hypotension, weight loss, fatigue, weakness, and confusion.[8]

Gonadotropin

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have important roles in reproduction with deficiencies affecting testosterone and estrogen levels in males and females, respectively. Generalized disturbances in mood and fatigue may occur. In both sexes, this may result in decreased lean body mass, bone mineral density, lower libido, sexual dysfunction, muscle weakness, and depression.[9] Females may additionally develop menstrual irregularities including amenorrhea and genitalia effects such as skin thinning (lichen sclerosus) or vaginal dryness.

Growth Hormone (GH)

As the name suggests, GH is essential for the normal physiologic growth of tissues and bone. It is the most common hormonal deficiency following TBI[10] causing cognitive, psychosocial, and physical health impairments. Individuals may have difficulty with attention, motivation, higher rates of depression, and social isolation;[11-12] in addition, there are negative impacts on cardiovascular health, exercise capacity, lean body mass, and bone mineral density.[9]

Prolactin

Prolactin is important for breast development and lactation. TBI can lead to elevated or depressed levels of prolactin, with hyperprolactinemia causing suppression of the gonadal axis. Thus, excess prolactin may present similarly to gonadotrophin deficiency as detailed above. Elevated levels may also result in galactorrhea in non-breastfeeding females and males.[13]

Thyroid Stimulating Hormone (TSH)

TSH stimulates the thyroid gland to regulate thyroid hormone (T3 and T4) production and to maintain the body's metabolism, growth, and development. Deficiency leads to many wide-ranging symptoms that may include fatigue, weight gain, hair and skin changes and cold intolerance. Neuropsychological disturbances may occur and negatively impact memory, executive functioning, and processing speed.[9,14]

Antidiuretic Hormone (ADH)

ADH is responsible for regulating water balance by acting on renal tubules to reduce water loss and maintain serum osmolality and circulating blood volume.[15] In diabetes insipidus, individuals present with symptoms of polyuria and polydipsia with resulting dehydration and hypernatremia.[16] These electrolyte disturbances occur in the first few days following trauma and are less common in chronic TBI, though persistent DI has been observed months following initial moderate to severe TBI.[17] Hyponatremia may develop from excess ADH through the syndrome of inappropriate antidiuretic secretion (SIADH).

Oxytocin

Oxytocin stimulates uterine contractions during labor and milk letdown following delivery in females.[18] As there are no confirmed adverse effects related to oxytocin deficiency, it is not currently of clinical relevance to post-TBI outcomes.

Diagnostic Work-Up and Management

According to the most recent consensus statement from the American Association of Clinical Endocrinologists and American College of Endocrinology, all individuals with moderate to severe TBI require evaluation of pituitary function during both the acute and chronic course of their recovery .[19] Additionally, symptomatic individuals with mild TBI are at risk for hypopituitarism and should undergo neuroendocrine testing. The time course of TBI rehabilitation and recovery is ideal for physiatrists to be the first to identify symptoms and drive appropriate evaluation. Physiatrists should take ownership of pituitary function screening to expedite care in tandem with referral to endocrinologists. Interpretation of abnormalities and subsequent hormone replacement therapy, if indicated, should be driven by the receiving endocrinologist.

Approach to Management of Chronic Post-traumatic Hypopituitarism (≥ 3 months after TBI)

Presentation of chronic PTHP is often challenging to interpret. Signs and symptoms are nonspecific with indolent presentations including vague constellations of observations such as fatigue, weight change, appetite loss, constipation, disequilibrium, irregular menses, temperature intolerance, neurocognitive or neuropsychiatric dysfunction, integumentary changes, joint aches, and/or hyponatremia. Additionally, multiple hormone dysregulations may contribute simultaneously, further confounding clinical diagnostic capacities in the absence of supporting laboratory data. Derangements in pituitary hormones

can generate an array of clinical sequelae which overlap with direct consequences of a brain injury itself or other pathologies such as primary end-organ dysfunction, and neuropsychiatric disorders.

Assessment of hormonal contributions to suboptimal neurofunctional status after brain injury is accomplished with diagnostic testing. Moderate to severe TBI individuals are at highest risk for chronic pituitary dysfunction and should be screened in the outpatient setting. Studies indicate that pituitary dysfunction can vary over time with some deficiencies resolving and others newly appearing regardless of acute pituitary hormone screen status.

`A consensus guideline or evidence-based timeline on when to perform neuroendocrine screening does not exist, but between 3- and 12-months post-injury is a reasonable range to consider. [19-21] A pragmatic consideration is to let clinical decision-making drive the choice to screen prior to 12 months post-injury and, if no screen has been performed by that time, to empirically screen at that juncture. Individuals with moderate to severe TBI, particularly those with pituitary injuries identified on neuroimaging, warrant earlier empiric testing due to increased risk. It has been suggested that, if no hormone deficiencies are present at 12 months post-injury, moderate and severe TBI survivors do not require further screening, but individuals with mild TBI may merit annual screening for 5 years;[20] however, the evidence supporting any strict schedule for monitoring is controversial due to variable quality of underlying the data.[22] A suggested approach/flowchart to evaluating PTHP in the outpatient setting is shown in Figure 2.

Pituitary Function Diagnostic Testing

Many diagnostic tests are available to interrogate post-traumatic pituitary function and are summarized in Table 2. Serum diagnostic tests exist to evaluate all pituitary hormones and to evaluate end-organ hormone levels which depend on pituitary contributions for intact neuroendocrine axis function (ex: adrenals, thyroid, gonads). Pituitary abnormalities on MRI have similar prevalence to serum-lab-diagnosed post-traumatic hypopituitarism.[23] MRI can visualize structural pituitary abnormalities such as enlargement, atrophy, infundibular transection, hemorrhage, or edema, but relationships between these findings and functional pituitary alterations have yet to be established.[23]

During the acute post-injury period, the focus should be on the hypothalamic-pituitary-adrenal (HPA) axis, with concern for secondary hypoadrenalism[24-25] and derangements in sodium management secondary to posterior pituitary dysfunction including diabetes insipidus and SIADH. Chronically, more thorough evaluation including anterior pituitary function is recommended.[19]

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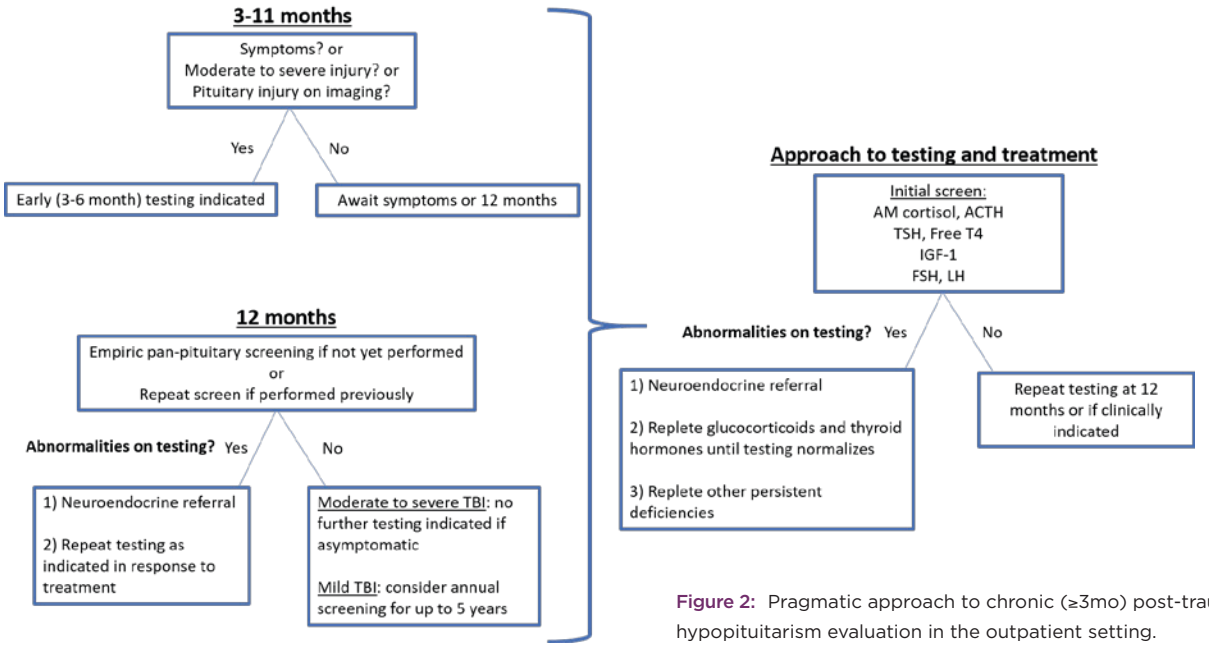

Figure 2: Pragmatic approach to chronic (≥3mo) post-traumatic hypopituitarism evaluation in the outpatient setting.

Table 2: Summary of diagnostic testing, interpretation, and other considerations for assessment of post-traumatic hypopituitarism. Please note that interpretation values are based on published cut points common to many assays in widespread use, but lab reference values may vary between institutions.

Pituitary Function	Test	Interpretation	Other considerations
Pituitary adrenal axis	Morning fasting serum cortisol	≤ 3 μg/dL diagnostic for hypoadrenalism; serum cortisol ≥ 18 μg/dL assures sufficient function. Otherwise, intermediate, further testing needed.	Can be confounded by steroids, acute illness, food intake, smoking, low body weight, stress
	Cosyntropin stimulation test (250 mcg)	Peak serum cortisol < 18 μg/dL diagnostic for hypoadrenalism.	Not reliable for several weeks after TBI
	Insulin tolerance test	Peak serum cortisol < 18 μg/dL diagnostic for hypoadrenalism.	Contraindicated with history of seizure, CVD, or advanced age.
	Morning fasting ACTH	Levels are low or inappropriately normal in secondary hypoadrenalism	
Pituitary thyroid axis	TSH	Low or inappropriately normal in secondary hypothyroidism	Can be confounded by thyroxine, amiodarone, heparin products, acute illness, pregnancy. May not emerge for weeks after TBI due to long half-life of T4.
	Free T4	Low in hypothyroidism	
Pituitary gonadal axis	Free testosterone (or total with SHBG) in men; estradiol in women	Low in hypogonadism	Menstrual history essential for context in females. Can be confounded by systemic steroids or opioids.
	FSH, LH	Low or inappropriately normal in secondary hypogonadism	
Growth hormone	IGF-1	Low with history of pituitary compromise + ≥ 3 other pituitary deficiencies is diagnostic of GH deficiency	Age- and gender-adjusted normative values. Assess only after other axes corrected.
	Insulin tolerance test or glucagon stimulation test	Peak GH <3 ng/mL is diagnostic for GH deficiency	Lower cut points in elderly and obese individuals
	GHRG-arginine stimulation test	Low is diagnostic of GH deficiency	Different cut points based on BMI
Posterior pituitary function	Serum + urine sodium and serum + urine osmolality	Hypernatremia with urine osmolality <700 mOsm/kg with polyuria is consistent with diabetes insipidus (ADH deficiency). Hyponatremia with serum osmolality <280 mOsm/kg and urine sodium >20 mEq/L with urine osmlolality >100mOsm/kg is consistent with SIADH.	Free water restriction improves SIADH while isotonic fluid administration either worsens hyponatremia or leaves it unaffected.
	Water deprivation test	Hypernatremia with peak urine osmolality <700 mOsm/kg after 8h water deprivation / 5% body weight loss with polyuria is consistent with diabetes insipidus. Improvement of hyponatremia with water deprivation is consistent with SIADH.	Dosing desmopressin sharply raises urine osmolality in central but not peripheral secondary DI

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Physiatrists are best-positioned and most likely to initiate neuroendocrine evaluation in the chronic setting, where an array of testing is available. The **pituitary-adrenal axis** can be assessed with morning serum cortisol, cosyntropin stimulation testing, insulin tolerance testing, and serum ACTH levels. The **pituitary-thyroid axis** is routinely assessed via serum TSH and Free T4. The **pituitary-gonadal axis** is assessed with serum FSH, LH, and either total testosterone and sex hormone binding globulin (or free testosterone) in men or estradiol in women but can be confounded by systemic steroid or opioid medications.[19] **Growth hormone** is assessed with serum insulin-like growth factor 1 (IGF-1), insulin tolerance or glucagon stimulation testing, and GH-releasing hormone-arginine stimulation testing. Notably, the insulin tolerance test is contraindicated in individuals with seizures, cardiovascular disease, or advanced age, and GH status should not be formally interpreted until after any other co-existing pituitary hormone deficiencies have been repleted.[19] Each test assesses a subcomponent of anterior pituitary function, while **posterior pituitary function** specific to ADH can be assessed with serum and urine sodium and osmolality, in addition to water deprivation testing. Posterior pituitary hormone oxytocin is not routinely assessed, despite its implication in neuropsychiatric and psychosocial dysfunction,[26] which are common after TBI. **Initial screens by the physiatrist can be completed with a single morning fasting blood draw including the following serum labs focused on anterior pituitary function: cortisol, ACTH, TSH, Free T4, FSH, LH, free testosterone (males) or estradiol (females), and IGF-1.**

Impact of Hormone Replacement

In chronic TBI, hormone replacement therapy is typically initiated in a stepwise approach under the guidance of an endocrinologist, starting with thyroid hormone and glucocorticoid replacement if one or both are present. After a period of weeks to months, repeat laboratory testing is performed and doses are optimized until stable, normal levels are reached. Once thyroid and glucocorticoid levels are well-managed, residual deficiencies may be addressed. For individuals with brain injuries, growth hormone deficiency is the most common chronic steroid hormone deficiency with prevalence variably reported, ranging from 10-63.6%.[27] The evidence base is limited for cognitive and rehabilitative responses to hormone replacement (and absent for many hormones), but growth hormone replacement therapy has demonstrated initial promise in small clinical studies for improving cognitive and functional rehabilitative endpoints.[28-31]

Clinical Vignette Outcome

AP was prescribed dantrolene 25mg TID with monitoring of her liver function tests (baseline testing was normal) to address her lower extremity spasticity. This medication was selected to minimize sedating side effects that could be observed with centrally acting medications. Additionally, her physiatrist ordered a neuroendocrine panel including TSH, free T4, FSH, LH, morning cortisol, and prolactin. Her blood work was consistent with post-traumatic hypopituitarism.

AP was then referred to an endocrinologist. She was started on hydrocortisone 10mg BID and levothyroxine 50mcg daily. Despite dose adjustments, she had recurrent apparent hypoglycemic and orthostatic episodes and was started on fludrocortisone 0.05mg daily for blood pressure support. Continuous glucose monitoring was incorporated for closer, proactive day-to-day management. Following repeat neuroendocrine panel, she was initiated on growth hormone replacement with somatropin 0.2mg subQ daily with significant improvement in hypoglycemic episodes. Laboratory readouts to assess response to hormone supplementation normalized over the ensuing weeks to months, concordant with ongoing improvements in energy levels and overall perceived health status and physical functioning. After 10 months of persistent amenorrhea, estradiol/progesterone supplementation was initiated with return of menses 5 months later. In addition to hormone replacement titration, AP continued to follow with PM&R brain injury for spasticity management. Her dantrolene was gradually up titrated to 75mg TID and she received localized botulinum toxin injections to address hamstring spasticity.

AP reengaged with physical therapy with less spasticity and improved energy enhancing her participation and tolerance. Her most recent PT assessments demonstrated improved motor control, somatosensory organization, and static and dynamic balance. She successfully met her goals and transitioned to a home exercise program.

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