

A Narrative Review on Posttraumatic hypopituitarism: predictors and useful Algorithms for Investigations and Treatment (Part-2)

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ABSTRACT

Introduction: Post-traumatic hypopituitarism (PTHP) is an important but often underdiagnosed consequence of traumatic brain injury (TBI), manifesting in both acute and chronic phases. In the acute phase, adrenal insufficiency (AI) may mimic symptoms of TBI and, if untreated, can be life-threatening. During the chronic phase, growth hormone deficiency (GHD) and other hormonal abnormalities may emerge. Awareness among emergency and acute care clinicians remains low, underscoring the need for simple, evidence-based diagnostic and management algorithms.

Objectives: To review current literature on the predictors, diagnosis, and management of PTHP, and to create practical clinical algorithms to guide timely recognition and treatment.

Methodology: A narrative review of cohort studies, case-control studies, systematic reviews, and meta-analyses published from 2007 onwards was conducted using PubMed, EMBASE, and Medline.

Results: Predictors of PTHP include severe TBI, intracranial hypertension, seizures, and intracranial bleeding. Cortisol measurement at 8:00 a.m. during the first 7 days post-TBI is the preferred test for diagnosing acute hypocortisolism, although random cortisol levels may be used when clinical suspicion is high. Approximately 50-75% of patients recover normal pituitary function within one year. Hormone replacement therapy is the cornerstone of management, following standard hypopituitarism protocols. Longitudinal follow-up at 3, 6, and 12 months is essential to detect delayed hormonal deficiencies.

Conclusion: PTHP is a significant sequela of TBI that requires heightened clinical awareness and structured management. Early diagnosis and intervention can be lifesaving in acute AI and improve outcomes in chronic hormone deficiencies. Two practical algorithms were developed to assist clinicians in evaluating and managing PTHP. Further research is needed to clarify predictive factors and long-term outcomes.

KEY WORDS: Post-traumatic hypopituitarism, Traumatic brain injury, Adrenal insufficiency, Growth hormone deficiency, Hormone replacement therapy.

INTRODUCTION

Traumatic brain injury (TBI) is a major contributor to morbidity and mortality worldwide. Post-traumatic hypopituitarism (PTHP) is a form of acquired

hypopituitarism after TBI. PTHP captured increased interest of the medical professionals in the last years. While the incidence and prevalence rates of PTHP are still ranged differently by many authors, clinicians' interest is more about how to properly and timely diagnose and

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treat such patients. Large numbers of post TBI patients are seen in OPDs and IPDs daily but not all of them required hormonal assessment. Despite this, a considerable number develop acute glucocorticoid deficiency and central diabetes insipidus in the acute phase, which need emergent intervention.¹ Thus, choosing the right category of patients in a timely manner for investigations and treatment during both phases of TBI is of paramount importance. Because health care professionals are lacking this knowledge and no ready to use clinical algorithms to approach TBI cases,² we carried this narrative review to raise clinicians' level of awareness of the endocrine aspect of TBI as well as creation of easy-to-use algorithms for investigations and treatment of PTHP cases. We divided it into two parts. This part dealt with the predictors, the created algorithms of diagnosis and treatment, and prognosis of PTHP. In part 1 of this topic, definitions and classifications, epidemiology, pathophysiology and clinical presentation of TBI were discussed. The need for neurosurgery in TBI, severe TBI, radiological findings, among other determine risk of developing PTHP.²⁻⁶

Predictors of post-TBI pituitary dysfunctions: Since it is unrealistic to do regular follow-up and hormonal assays for all TBI patients, it is imperative to determine predictive factors for post-TBI hypopituitarism.¹ These factors include type and severity of injury, acute endocrine dysfunction after TBI, need for neurosurgical intervention, and initial clinical and radiological parameters.²⁻⁶

Nemes and colleagues prospectively evaluated the potential risk factors resulting in development of pituitary hormone dysfunction amongst TBI survivors ($n=126$) on long-term follow-up.⁴ The severity of head injury was found to be an independent factor that predicts all hormone dysfunctions. Accordingly, cases with severe injuries were at a higher risk of developing PTHP as compared with those with mild to moderate brain injuries.⁴

Diffuse axonal damage, elevated intracranial pressure, motor vehicle crush types of injuries⁷ as well as fractures base of the skull and other severe acute abnormalities detected by CT scan of the brain after trauma, were reported as the radiological parameters that can predict pituitary failure.^{2,5,8} Intracranial bleeding and hemorrhage are good predictors for GHD and central adrenal insufficiency (CAI) as reported by Gray and colleagues' review in 2019.² However, Nemes et al did not find a link between the type of head injury or the presence of fracture base of skull and the development of hormonal deficits.⁴

Other researchers observed that raised ICP is a well noted predictor of occurrence of PTHP.²⁻⁴ Contrary to this, Olivecrona and colleagues failed to find a connection between raised ICP and occurrence PTHP during the acute phase of TBI.⁹

The need for surgical intervention following TBI (in particular, the insertion of external ventricular drain -EVD) predicted the occurrence of both growth hormone (GH) deficiency (Odds Ratio (OR) 9.33) and GH

insufficiency compared with those who received non-invasive critical care. This implies the pathogenic role of increased ICP in the hindrance of secretion of GH leading to its deficiency. Even so, none of the other hormonal deficiencies was linked to this factor.⁴

Early pituitary dysfunctions in the acute phase do not necessarily predict occurrence of future hormonal defects.^{4, 10} However, the endocrine function should be assessed from time to time, starting from one-year post TBI in some selected patients especially those with severe head injuries as well as those who receive invasive surgical interventions as part of their management.⁴

Advanced age at the time of trauma,^{2,3} hypotension,^{2,11} intubation for more than ten days, hypoxia, hospital admission and duration of coma were additional factors that predict occurrence of PTHP.²

According to Schneider et al in a prospective study, no single predictor is exclusively associated with deficiency of only one pituitary axis, but all impairments of all pituitary axes can appear simultaneously.⁶ Factors that predict hypopituitarism among post TBI survivors are shown in Table-I.

Diagnosis

Selection of TBI patients for PTHP screening: Selection of patients for screening for PTHP remains a dilemma especially in the acute phase when there might be overlap between symptomatology of TBI and PTHP. Furthermore, the initial abnormalities can resolve spontaneously because some of these changes are part of an acute stress response as well as adaptive reactions to trauma. Another point is that the drug use and surgery done during this phase may contribute to the conundrum.² These factors in addition to the potentially serious clinical consequences of failure to diagnose hypopituitarism (especially hypoadrenalism during the acute phase of TBI), mandate for due diligence for screening not only in terms of candidate selection, but also in terms of timelines and screening methods, as diagnostic accuracy is key for appropriate management.¹⁵ Table-II shows categories of post-TBI eligible for PTHP screening.

Hormonal assay

Acute phase assay. Biochemical diagnosis of PTHP and cut-off values for PTHP: In asymptomatic patients not requiring admission after TBI, no hormonal assay is needed during the acute phase. If, by three months they remain asymptomatic, they should be reassured. However, testing should be carried out if symptoms are present.¹⁵

A morning serum cortisol level (8-9 a.m.) on day 1-7 after trauma is the first line test to assess for adrenal insufficiency.^{12,20,21} Patient must be cannulated before 30 min of blood withdrawal.²² Recently, some authors supported the use of random cortisol level when there is a strong suspicion of adrenocorticotrophic hormone (ACTH) deficiency after TBI when waiting for the recommended 8:00 a.m serum cortisol would delay the diagnosis and management of adrenal insufficiency (AI).²² On other hand, some authors believe that random cortisol levels may not indicate the proper status of the patient.^{18,20}

Table-I: Factors Forecasting Occurrence of Post-TBI Hypopituitarism.^{2,4,6,7,11-14}

<i>Predicting factor</i>	<i>Following hormone defect(s)</i>	<i>Authors, year</i>	<i>Study Design/ sample size (n)</i>
Penetrating (open) injury	DI	Hadjizacharia et al (2008) ¹¹	Prospective study, n=436; severe TBI
Diffuse axonal injury	PTHP	Schneider et al (2008) ⁶	Prospective study, n=78; mild-severe
Intracranial bleeding/ hemorrhage	DI	Hadjizacharia et al (2008) ¹¹	Prospective study, n=436; severe TBI
	GHD, CAI	Gray et al (2019) ²	A review
	CAI	Silva et al (2015) ⁷	Retrospective study; n=166
Skull fracture	Anterior pituitary insufficiency/ deficiency (all axes)	Tanriverdi et al (2015) ¹²	Systematic review, 16 studies; n=1291
	Anterior pituitary insufficiency/ deficiency (all axes)	Lauzier et al (2014) ¹³	A systemic review, 66 studies; n=5386
	PTHP	Schneider et al (2008) ⁶	Prospective study, n=78; mild-severe
Severity of injury	GHD	Casano-Sancho et al (2013) ¹⁴	Prospective study, n=23 (children above 6 years old)
	GHD/GHI	Nemes et al (2015) ⁴	Prospective study, n=126
	Anterior pituitary insufficiency/ deficiency (all axes)	Lauzier et al (2014) ¹³	A systemic review, 66 studies; n=5386
	PTHP	Klose et al (2007) ³	A cross-sectional cohort study, n=104
	DI (GCS ≤ 8, AIS Head > 3)	Hadjizacharia et al (2008) ¹¹	Prospective study, n=436; severe TBI
Surgical intervention	GHD	Nemes et al (2015) ⁴	Prospective study, n=126
Hospital admission time	GHD	Gray et al (2019) ²	A review
High ICP	GHD	Nemes et al (2015) ⁴	Prospective study, n=126
	Anterior pituitary insufficiency/ deficiency (all axes)	Klose et al (2007) ³	A cross-sectional cohort study, n=104
Brain edema	DI	Hadjizacharia et al (2008) ¹¹	Prospective study, n=436; severe TBI
Older age	Anterior pituitary insufficiency/ deficiency (all axes)	Lauzier et al (2014) ¹³	A systemic review, 66 studies; n=5386
	PTHP	Schneider et al (2008) ⁶	Prospective study, n=78; mild-severe
Motor vehicle crush	TSH deficiency, ACTH deficiency	Gray et al (2019) ²	A review
	ACTH deficiency	Silva et al (2015) ⁷	Retrospective study, n=166
Intubation days	PTHP	Klose et al (2007) ³	A cross-sectional cohort study, n=104
Presence of APA/ AHA	PTHP	Tanriverdi et al (2015) ¹²	Systematic review, 16 studies; n=1291
Obesity	GHD	Klose et al (2007) ³	A cross-sectional cohort study, n=104
Post-traumatic seizures	CAI	Gray et al (2019) ²	A review
	CAI	Silva et al (2015) ⁷	Retrospective study, n=166

Table-II: Categorization of post-TBI patients into groups for PTHP screening.^{2,12,16-19}

Categorization of post-TBI patients into groups for PTHP screening recognition					
Patients required testing for PTHP			Patients not required testing for PTHP		
All patients with symptoms (except patients with poor prognosis)	Discharged TBI patients or those admitted for a short period of less than two days in the presence of symptoms of adrenal insufficiency (low sodium, low blood pressure and low blood glucose)	Patients (mild to severe TBI) who have one or more of following: -Radiological changes -Presence of adrenal insufficiency and central diabetes insipidus -Being admitted for more than 2 days -ICU admitted -Requiring neurosurgery -Repetitive mild TBI in certain patient populations like sportsmen -Blast related injuries -Presence of antibodies (APA/AHA)	Patients with mild TBI without symptoms and overburden factors	Discharged patients with mild TBI without loss of consciousness and/or short time post traumatic amnesia (less than half-an-hour)	Patients with poor prognosis: -Vegetative state -Severely disabled -Low life expectancy

Table-III summarizes the laboratory cut-off values for diagnosis of PTHP and tests administration.

Standard corticotropin dynamic test is a preferable choice as an additional test.²⁰ Most of the authors agree that cortisol levels above 500 nmol/l indicate a normal response.^{1,12,20} Gilis-Januszewska and colleagues proposed that when the morning cortisol level is between 85 nmol/l and 500 nmol/l, Short Synacthen Test (SST) should be performed to confirm the presence of adrenal insufficiency.²¹ Klose et al noted that analyzing cortisol by using a polyclonal antibodies mass spectrometry, can establish the cut-offs for cortisol in the 350–420 nmol/l range.²⁹

In addition, 250 µg corticotropin dynamic test can be applied to diagnose adrenal insufficiency in patients already receiving empiric glucocorticoids to reduce intracranial pressure. Suppressed cortisol response to stimulation at 60 minutes may indicate AI in such situations.³⁰

Low dose corticotropin SST dynamic test was highlighted in ESE guidelines of year 2016 as one of the stimulation tests especially in paediatric patients.²⁰ However, it has gained reduced popularity in the recent years among researchers despite having similar sensitivity to the standard synacthen test. This is due to the unavailability of the 1mcg corticotropin preparation necessitating dilution of the 250 mcg preparation, which is cumbersome and prone to errors.³¹

To diagnose secondary adrenal insufficiency, insulin tolerance test (ITT), a dynamic test, can be used. However, it must be performed by a qualified personnel under a strict medical protocol. It should be avoided in those patients with ischemic heart disease, cardiac arrhythmias, history of epilepsy or presented seizures.^{1,32}

Some authors prefer to avoid this test in the acute phase of TBI altogether.³³ It can be hazardous in children with structural brain changes and in elderly patients due to hypoglycemia risk.³²

Glucagon dynamic test is administered with 1 mg glucagon IV¹ or IM.²⁰ To avoid overestimating the results of hypocortisolism on GST, patients should be assessed further with SST.

The diagnosis of acute hypocortisolism is also weighed down by divergence between total plasma cortisol levels and free cortisol levels because of fluctuations in cortisol binding globulin (CBG) levels.¹

In the diagnosis of central DI, classic water deprivation test (WDT) followed by administration of desmopressin should be performed in the presence of confirmed hypotonic polyuria. Polyuria is defined as a urinary volume above 50 ml/kg per 24 hours or 3-4 L per 24 hours in adults, while hypotonic urine is urine with an osmolality of less than 300 mOsm/Kg.^{20,27} The reasons for hypotonic polyuria other than central DI must be excluded. These reasons include medications, hyperglycemia, hypercalcemia, hypokalemia, renal disease, thyrotoxicosis and primary polydipsia. Urine osmolality above 800 mOsm/Kg prior to the test excludes DI.²⁷

According to Kgosidialwa and colleagues, GH assessment is not reasonable in the acute phase as GH level may recover spontaneously in those with GHD.¹⁷

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) should be suspected by the presence of these criteria:¹

- Urine osmolality of more than 100 mOsm/kg,
- Urine osmolality of more than 100 mOsm/kg and,
- Urine sodium above 40 mmol/L.

Table-III: Biochemical Diagnosis of PTHP and Cut-off Values for PTHP: 14,12,20,21- 28

Hormone test	Test	Deficiency	Borderline		Normal response
HPA axis (Hypo-thalamic-Pituitary-Adrenal axis)	Morning (8-9 a.m.) cortisol	Cortisol <83-100 nmol/L (or <3 µg/dL) (21,12)	Cortisol values between 85-500 nmol/L (3- 18 µg/dL) need further investigation (21)		Cortisol >500 nmol/L (11,12, 21)
Random serum cortisol		<500 nmol/L (1)			
GST					
SST (Corticotropin (ACTH) low dose (1 µg) test	<414 nmol/L (<15 µg/dL) (22)			>938 nmol/L (>34 µg/dL) (22)	
Corticotropin (ACTH) standard dose (250 µg) test	Cortisol <500 nmol/L (4,12)			Cortisol >450 nmol/L (1)	
ITT				>500 nmol/L (12)	
	Cortisol <500 nmol/L (20)			>500 nmol/L (1)	
				Cortisol should be at 30 min >500 nmol/L (18.1 µg/dL) (20)	
	Cortisol <500 nmol/L (20)			Cortisol should be at 30 or 60 min >500-550 nmol/L (>18.1-20 µg/dL) (20)	
				Peak cortisol >500 nmol/L (4,12)	
	Cortisol <500 nmol/L (4,20)			Peak cortisol >500-550 nmol/L (>18.1-20 µg/dL) (20)	
HPA axis (Hypo-thalamic-Pituitary-Thyroid axis)	Low or normal TSH in combination with low fT4 and low or normal TSH diagnose central hypothyroidism (14,74)	fT4 <11 pmol/L (12) fT4 <12 pmol/L (0.93 ng/dL) (4)			

HPS axis (Hypo-thalamic-Pituitary-Somatotropic axis)	GH overnight test	peak serum GH level			peak GH level	
		<5ng/mL ⁽²³⁾			>5ng/mL ⁽²³⁾	
GHRH+ Arginine test (cutoffs for GH response are BMI related)	GH <4µg/L ⁽¹²⁾ , <5 ng/mL adult, <7 ng/mL children ⁽²³⁾			GH should be >4 µg/L ⁽¹²⁾ , >5 ng/mL adult, >7 ng/mL children ⁽²³⁾		
	peak GH <11 µg/L at BMI <25 kg/m ² , peak GH <8 µg/L at BMI 25-30 kg/m ² , peak GH <4 µg/L at BMI >30 kg/m ² ⁽²⁴⁾					
	GH <3 ng/mL ⁽⁴⁾ <3 µg/L ⁽²⁰⁾			GH should be >3-5 µg/L ⁽²⁰⁾ , >5 µg/L adult ⁽²⁵⁾		
	GH ≤3 µg/L ⁽¹²⁾ , <3 ng/mL severe ⁽¹⁾ , <5 ng/mL adult, <7 ng/mL children ⁽²³⁾	moderate 3-5 ng/mL ⁽¹⁾		GH >3 µg/L ^(12,20) >5 ng/mL adult ^(1,23) , >7 ng/mL children ⁽²³⁾		
Macimorelin test GHRH+ Pyridostigmine test (cutoffs for GH response are BMI related)	GH 3 µg/L for normal weight patients, 1 µg/L for obese patients ⁽²⁵⁾ GH <2.8 µg/L ^(25,26)			GH >2.8 µg/L ^(25,26)		
	peak GH <11 µg/L at BMI <25 kg/m ² , peak GH <8 µg/L at BMI 25-30 kg/m ² , peak GH <4 µg/L at BMI >30 kg/m ² ⁽²⁴⁾					
HPG axis (Hypo-thalamic-Pituitary-Gonadal axis)	LH, FSH, Testosterone (male)	LH ≤8.6 U/L; FSH ≤12.4 U/L; Testosterone <9.9 nmol/L (2.85 ng/mL) ⁽⁴⁾			LH >8.6 U/L; FSH >12.4 U/L; Testosterone >9.9 nmol/L (2.85 ng/mL) ⁽⁴⁾	
	LH, FSH (female below 50 years old)					
	LH, FSH (female above 50 years old)					
	LH ≤1.7 U/L and FSH ≤1.5 U/L ⁽⁴⁾			LH >1.7 U/L and FSH >1.5 U/L ⁽⁴⁾		
	LH ≤15 U/L and/or FSH: ≤15 U/L ⁽⁴⁾			LH >15 U/L and/or FSH: >15 U/L ⁽⁴⁾		

Posterior pituitary function/ ADH	Urine osmolality/plasma osmolality ratio			ratio should be ≥ 2 ⁽²⁶⁾
WDI (diuretics, GCs, NSAIDs, SGLT-2 inhibitors, carbamazepine, chlorpropanide interact with test)	urine osmolality of <300 mOsm/Kg with plasma osmolality >300 mOsm/L confirms DI ⁽²⁷⁾ plasma osmolality >295 mOsm/L ⁽²⁰⁾ After DDVAP: Urine concentrates >800 mOsm/kg ⁽²⁰⁾ An increase of at least $>50\%$ in urine osmolality suggests complete central DI (the increase can be up to 200% to 400%) ⁽²⁷⁾	Urine osmolality $300\text{--}800$ mOsm/kg ⁽²⁰⁾	Urine osmolality $>800\text{--}1200$ mOsm/Kg in deprivation phase is exclude DI ⁽²⁷⁾	
	ITT: Patient must be admitted in a ward and be supervised the whole time. Patient overnight fasting. At 8 AM forearm canula must be inserted. After 30 minutes administered IV regular insulin in dosage $0.05\text{--}0.15$ U/kg. Glucose should drop lower than 40 mg/dL (2.2 mmol/L). Glucose, GH, and Cortisol must be measured at $-30, 0, 30, 60$, and 120 minutes ⁽²⁰⁾. Low-dose SST: Cosyntropin (ACTH 1-24) administered in dosage 1 μg IV. Blood collected at 0 and 30 min for cortisol ⁽²⁰⁾. Corticotropin standard dose (250 μg) test: Cosyntropin (ACTH 1-24) administered in dosage 250 μg IM/IV. Blood collected at $0, 30$, and 60 min for cortisol ⁽²⁰⁾. GH overnight test: blood samples for every 20 min from 8 PM till 8 AM. Comparing with healthy children sampling ⁽²³⁾. GST: glucagon administered as 1 mg IM (if weight above 90 kg, 1.5 mg), children 0.02mg/kg of glucagon. Blood GH and glucose measured at $0, 30, 60, 90, 120, 150, 180, 210$, and 240 minutes. Cutoffs should be correlated to BML, because obesity can blunt the response ^(20,23, 25). GHRH+Arginine test: GHRH administered in dosage 1 μg/kg IV (max 100 μg) at 0 minute, then followed by 10% arginine hydrochloride infusion 0.5 g/kg (max dose adult 35 gm, children 20 gm) over 30 min. Blood collected at $0, 30, 45, 60, 75, 90, 105$, and 120 min for GH. Cutoffs should be correlated to BML, because obesity can blunt the response ^(23,20). GHRH+Pyridostigmine test: Pyridostigmine administered 120 mg at -60 minutes, then GHRH administered in dosage 1 μg/kg IV at 0 minute. Blood collected at $-75, -60, 0, 20, 30, 45, 60$, and 90 min for GH. Cutoffs should be correlated to BML, because obesity can blunt the response ⁽²⁴⁾. Macimorelin test: Prepared macimorelin oral solution at a dose of 0.5 mg/kg administered within 30 minutes. Blood collected at $0, 30, 45, 60$, and 90 min for GH ⁽²⁶⁾. WDT: 8 AM. Start fluid deprivation for 8 hours ⁽²⁰⁾. Measure weight, urine output, urine and plasma osmolality every 2 hours, every voided urine must be recorded. Patient should take nothing by mouth. The dehydration phase should be abrupted in case: loss $>3\%$ of body weight, elevation of serum sodium $\geq 146\text{--}150$ mmol/L and orthostatic hypotension ⁽²⁷⁾. DDVAP administered in dosage 2 μg IM ⁽²⁰⁾ or IV/IM ⁽²⁷⁾ after 8 hours of deprivation. Patient can drink freely since this time. Dehydration phase least for 8 hours for complete DI and it can take less or more for non-DI reasons or incomplete DI. Stop test if $>3\%$ of weight loss registered.			

- There is inter-laboratory variability of the hormones profiles due to differing test assays.^{20,21} It is therefore, imperative to mention that no test in isolation can diagnose and accurately categorize all individuals with PTHP.²¹
- Accordingly, borderline cases need clinical evaluation as well as close follow-up.¹²

Long term assessment: Post hospital discharge:

Screening for pituitary dysfunction post TBI should be performed in all patients omitting those with asymptomatic mild TBI. The timing for screening should be at 3, 6 and 12 months post trauma and the schedule is as follows:

3rd and 6th months' assessment:

Adrenal: morning cortisol or dynamic tests (standard short synacthen test, ITT);^{12, 20}

Thyroid: Free T4 and thyroid stimulation hormone (TSH). For central hypothyroidism (CH) diagnostic of both tests should be done. Combination of low or low normal fT4 with low TSH may indicates diagnosis of CH.²⁹ Performing just TSH testing without fT4 is not sufficient.²⁸

Gonadal axis: FSH/LH/Testosterone for both sex.³³ In premenopausal females, the menstrual history should be inquired about. If deficiency present, hormonal replacement should be done and the test repeated at one year.

Posterior pituitary: plasma and urine osmolality, WDT.^{20,27}

One-year assessment: This includes the same tests as the ones done at 3 and 6 months in addition to prolactin (PRL) and GH assays.

GH assessment is deferred until one-year post TBI due to its complex axis¹⁵ and transient nature in the acute phase.²⁵ Kgosidialwa et al recommended GHD screening at six months to one-year after TBI for adults.¹⁷ Children should be screened earlier.³³ However, direct assaying of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) is unreliable for GHD diagnosis, instead, dynamic testing is preferred.^{17, 25, 33, 34} Patients should be tested for other pituitary deficiencies prior to GH replacement therapy and adequately replaced when necessary.^{20, 25}

Insulin Tolerance Test (ITT) is the optimal test for GHD screening with an upper threshold $>3-5 \mu\text{g/L}$;²⁰ $>5 \mu\text{g/L}$ ²⁵ in adults. In cases where ITT is contraindicated e.g., when there is a positive history of seizure, presence of CV disease or in elderly patients, other provocative tests can be conducted such as GST, macimorelin test,²⁵ GHRH-Arginine test, GHRH-Pyridostigmine test,²⁴ and L-dopa stimulation test. However, according to AACE 2019 guidelines, GHRH-Arginine test and L-dopa tests are less reliable compared with ITT, GST, and macimorelin tests.²⁵ Macimorelin test is considered safer as it does not require achievement of hypoglycemia. It also is less time and work-power consuming,²⁵ ITT, on the other hand, is more work-power consuming and in some cases can be considered unsafe.²⁶

In obese patients, BMI-related thresholds should be used for GHD diagnosis, as they are more accurate. Non-BMI related thresholds tend to overestimate GHD as noted by Silva and colleagues.^{7,29}

Molitch et al suggested that two tests are generally required to clarify IGHD diagnosis.³⁵ However, one dynamic test is sufficient to make a diagnosis in cases where other pituitary deficiencies were already confirmed.²⁴

Emelifeonwu et al in a meta-analysis stated that baseline hormone screening tests might be as much informative as the dynamic tests albeit at a cheaper cost, less labor intensive and not as time-consuming.³⁶ We created an algorithm to aid in the investigations for PTHP. (see Fig.1).

Treatment: Better survival rates can be realized when a multidisciplinary team that includes the neurosurgeons and endocrinologists is involved in the management of TBI patients.³⁷

When timely diagnosis of PTHP is made and appropriate management instituted, it affects positively on post TBI recovery and quality of life.³⁶ At one year post TBI, full recovery occurs in about 50% of those who developed hormonal deficiency within the first 6 month. There are individuals in whom the hormone deficiency occurs beyond one year following TBI.³⁸ Hormone replacement therapy may be required in some of the cases.

Hormone replacement therapy: The main stay of treating post-TBI hypopituitarism is hormonal replacement therapy, generally in a manner similar to treating central hypopituitarism of other etiologies.

In the acute phase: It is crucial to urgently identify and treat AI to avoid fatal outcomes.⁹ Post-TBI AI patients have high death rate and usually require more vasopressor medications.^{1,33,39} Immediate glucocorticoid therapy should be administered in all those with acute adrenal insufficiency (AI).^{21,37} 100 mg of Hydrocortisone (HC) as an intravenous bolus should be administered followed by HC 100-200 mg infusion in 5% dextrose water (D5W) or 25-50 mg intramuscular injection 6-hourly.⁴⁰ Tanriverdi and colleagues suggested a dose of HC as 50-100 mg IV every 8 hrs.¹² whereas, Garrahy et al recommended a dose of 200 mg of hydrocortisone parenterally in divided doses or as a continuous infusion to the unstable TBI patients while waiting for the investigations results if there is an associated hyponatremia, hypoglycemia or very low blood pressure.³⁷

In the acute phase post TBI it is important to consider central diabetes insipidus (CDI) and/or SIADH, as like AI, they are serious and life-threatening conditions.³³

Acute central diabetes insipidus appears in less than 2 days post-TBI.³⁷ If diagnosis of DI is confirmed, desmopressin (DDAVP) and fluid replacement should be promptly administered.³⁷ A single injection of DDAVP at a dose of 0.4-1 mcg should be administered intravenously or subcutaneously twice a day.^{37,41} Regular doses of DDAVP are required only if polyuria persists more

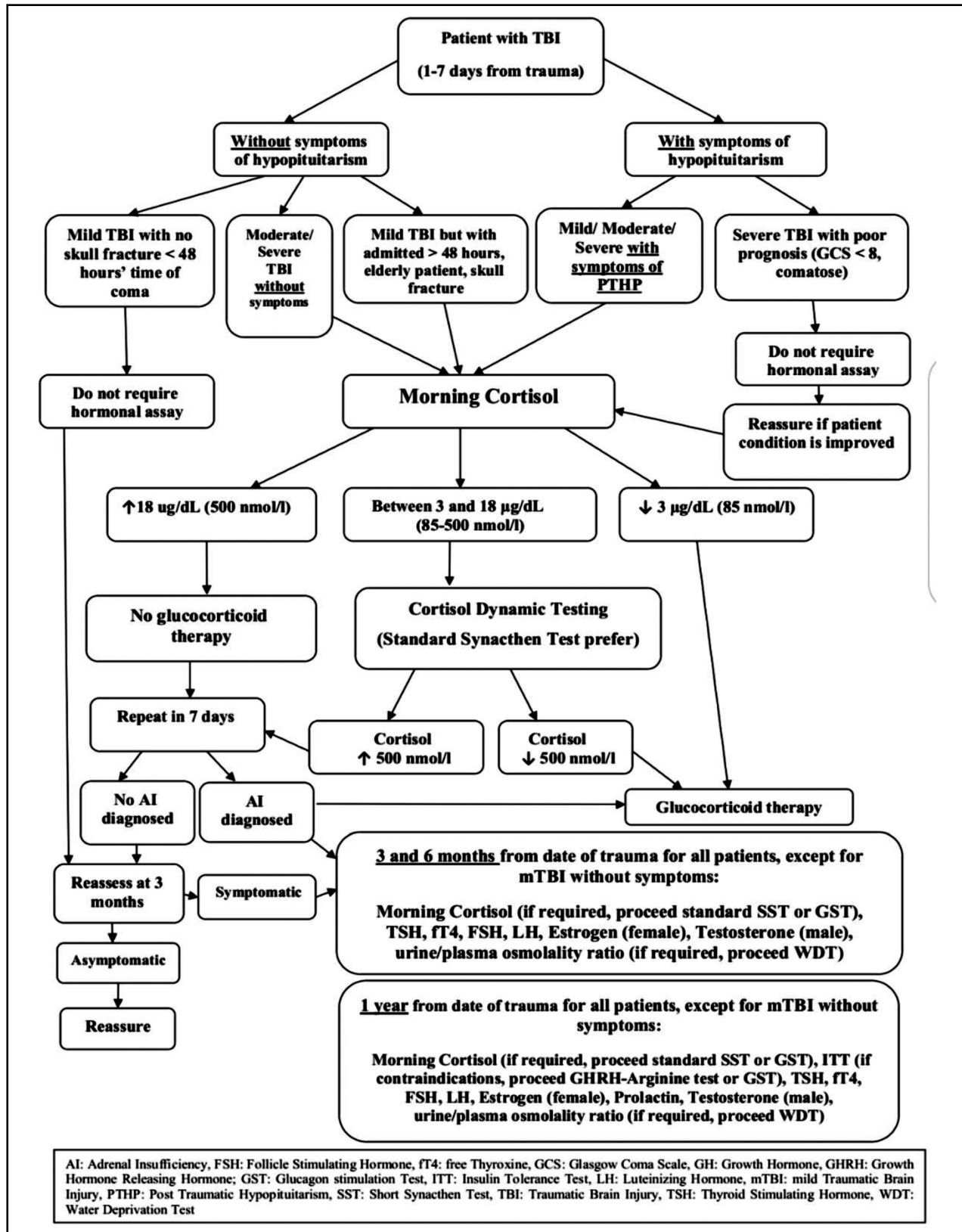


Fig.1: Investigation Algorithm
Created by referring to the following sources:^{2,15,16,21,22}

Table-IV: Prognosis of PTHP.^{1,9,11,17,21,34,41,52-55.}

<i>Factor</i>	<i>Influence on PTHP prognosis</i>	<i>Authors, year</i>
GHD	Linked to long-lasting adverse medical outcome. Patients with severe GHD have prolonged stay in ICUs	Kgosidialwa et al (2019) ¹⁷ , Kreber et al (2016) ³⁴
Cortisol	No correlation between values of serum cortisol in the acute phase and higher mortality rates at 3 months	Olivecrona et al (2013) ⁹
	Not associated with higher mortality rate	Wagner et al (2011) ⁵²
	Hypocortisolism in acute phase is a predictor of mortality	Hannon et al (2011, 2013) ^{1, 53}
High estradiol	Poor GOS at six months, higher mortality rate	Wagner et al (2011) ⁵²
High progesterone	Negative outcome, poor GOS in six months	Wagner et al (2011) ⁵²
High testosterone	Negative outcome, poor GOS in six months	Wagner et al (2011) ⁵²
Diabetes Insipidus	High mortality risk especially when not treated	Capatina et al (2015) ⁴¹
	Predicts mortality and carries a significant mortality risk	Hadjizacharia et al (2008) ¹¹
high LH and FSH levels in males	Correlated with negative outcome	Olivecrona et al (2013) ⁹
	Connected to higher mortality and proposed the use of LH value in the acute phase of TBI as a predictor of outcome in males	Hohl et al (2018) ⁵⁴
fT3	Low fT3 in the acute phase may predict poor GOS	Dalwadi et al (2017) ⁵⁵ , Olivecrona et al (2013) ⁹
Prolactin	High prolactin in the acute phase were not related to an increased mortality and neither a decreased score on the GCS nor on the GOS. Hyperprolactinemia is particularly likely to recover and therefore, cannot be used as a prognostic indicator.	Olivecrona et al (2013) ⁹
Severe TBI	Correlated with negative outcome	Gilis-Januszewska et al (2020) ²¹
Older age	Higher mortality rate	Wagner et al (2011) ⁵²
BMI	Not associated with higher mortality rate	Wagner et al (2011) ⁵²

than 48 hours.³⁷ Improper administration of DDAVP is dangerous and can lead to increased risk of brain edema, fluid overload, and seizures with consequent higher mortality rate. In addition, the patient's status can suddenly change from DI to SIADH causing more harm,¹¹

Triple-phase response is a rare event in which the first phase is characterized by signs of diabetes insipidus as polyuria with low urine osmolality. The second phase is characterized by SIADH with hyponatremia and a third phase of return to DI about two weeks later. Sodium and potassium should be monitored regularly while managing DI and should be corrected accordingly. Uncorrected hypokalemia may cause vasopressin-resistant polyuria.³⁷

It is not necessary to replace gonadotrophin hormones (FSH and LH) in this phase as these deficiencies tend to be transient in nature.²¹

In central hypothyroidism, thyroxine replacement is not required immediately in the acute phase as the T4 hormone has a long-half life in the body. In cases where its administration is warranted, it should be given after corticosteroid therapy.³⁷

In the chronic phase: The main stay of treating PTHP in the chronic phase is hormone replacement therapy (HRT) for the different hormone deficiencies present generally in a manner similar to treating hypopituitarism of other etiologies.²¹

In the chronic phase, patients with hypocortisolism should be reevaluated to exclude permanent AI, which if confirmed, should be treated with long-term hydrocortisone at 15-20 mg tablets taken in the mornings upon waking up. Extended-release HC formulation are available and can be used as an alternative to the standard HC.²⁰

In mild CDI, DDAVP can be administered in dosage of 0.2 mg orally at bedtime or gradually increase it up to 0.2 mg three times daily for severe DI.³⁷ Capatina et al.⁴¹ recommend oral (0.1-0.2 mg), sublingual (0.06, 0.12, 0.24 mg) or intranasal (0.01-0.04 mg) DDAVP formulations in patients with chronic DI. Different doses of DDAVP signify that the dose correlates to severity of DI.³⁷

Hemodynamically stable patients, whose sense of thirst is intact, can be managed conservatively by encouraging water intake. These patients should assess their urine output and self-administer DDAVP only when urine output is >250 ml/hr. Moreover, these patients should have regular tests for urine specific gravity, plasma and urine osmolality as well as plasma sodium concentration.

Aggressive water replacement should be avoided due to the risk of water intoxication associated with cerebral and pulmonary edema and dilutional hyponatremia.⁴¹

For those who are adipsic with no sense of thirst, it is recommended that they receive fixed doses of DDAVP and fluid replacement as guided by the plasma sodium concentration, urine/plasma osmolalities and body

weight. In addition, prophylaxis against venous thromboembolism is warranted.^{20,41}

Untreated GHD increases risk of cardiovascular morbidity and mortality.²⁵ Recently, several authors^{21,42-45} confirmed that GH replacement in the chronic phase is associated with enhanced quality of life (QoL), ameliorated BIAFAC symptoms (anxiety, fatigue, altered cognition, sleep disturbance), improved thinking process, strengthen body composition, and better exercise tolerance.

Mossberg and colleagues administered recombinant human growth hormone (rhGH) for two months to patients with post-TBI GHD that occurred more than one year after trauma.⁴⁴ There was a significant improvement in depression and fatigue as well as a notable increase in oxygen uptake and aerobic activity in those who received rhGH. Quality of Life in Adult Growth Hormone Deficiency Assessment (QoL-AGHDA) questionnaire should precede GH therapy and then every 12 months to evaluate QoL changes.²⁵ According to Kozlowski Moreau and colleagues, a TBI-specific questionnaire e.g., the Quality of Life after Brain Injury (QOLIBRI), should be used to assess GHD patients' QoL which takes into consideration the various domains of health-related QoL post TBI.⁴² QoL in post-TBI GHD patients under treatment is greater compared to GHD due to nonfunctioning pituitary adenoma (NFPA).³³

Before commencing rhGH therapy, one should take into consideration that GH interacts with other pituitary hormones that can necessitate thyroxine and glucocorticoids dose adjustment.²⁵ For those less than sixty years, the standard daily dose is 0.2-0.4 mg for and 0.1-0.2 mg per day for those above sixty years.²⁰ Doses of 0.4-0.5 mg per day can be used in patients younger than thirty years old.²⁵ Serum IGF-1, graded by age (SDS -2 to +2) should be used for rhGH dosage monitoring, along with blood glucose, lipid profile, thyroid function and BMI observation.²⁵ Titration of dosage should be done by 0.1-0.2 mg per day every 6 weeks towards a target of IGF-1 level below the ULN.²⁰ If improvement is achieved, treatment should be continued constantly, otherwise if no benefit observed in 1-2 years, therapy can be discontinued with 6 months follow-up.²⁵

In children, replacing growth hormone is recommended in the chronic phase post TBI due to its significant role in linear growth regulation, improved body and bone composition, normal vascular reactivity and tone, normal brain development in addition to central nervous system repair processes after brain injury.⁴⁶ Resolution of some of the cognitive impairments takes place with GH replacement in cases with GH deficiency or insufficiency, albeit it is partial.⁴⁵

Evidence is uncertain on the benefits of replacing sex hormones (testosterone in males and estrogen in females) on cognitive functions in individuals with PTHP. Garrahy and colleagues³⁷ and Fleseriu and

colleagues²⁰ suggested that sex hormone replacement therapy is beneficial on bone, muscle and sexual health. It is however important to consider the patient's value and preference regarding cost, parenting desires and convenience with treatment before administering this therapy.

The commonest delivery modes and regimens for testosterone replacement include Injections:

- Weekly 75-100 mg of testosterone enanthate
- Weekly testosterone cypionate
- Alternate week 150-200 mg of testosterone cypionate

Patches:

- 1 or 2 5 mg-testosterone patches
- applied at night on the skin (back, thigh or upper arm)
- Gels (sachet, tube or pump):
- 5 -10 g of 1% testosterone gel applied daily

Bio-adhesive buccal testosterone:

- 30 mg twice daily

Subcutaneous pellets:⁴⁷

- Placed for 3-6 months

Tablets:³⁸

- **Testosterone undecanoate:** 80-120 mg twice daily.

Monitoring of serum testosterone as well as symptoms evaluation should be done at 3-6 months intervals with the aim to achieve a medium range of normal serum testosterone values.⁴⁷

For females with decreased gonadal function post-TBI, HRT with an ethinyl estradiol at a daily dose of 2 to 4 mg³⁸ or OCP (combined estrogen-progestin) can be administered.²⁰ HRT should be administered until the mean age of natural menopause.³⁸ It is not beneficial to monitor gonadal function by serum E2.²⁰

For individuals with central hypothyroidism, oral levothyroxine replacement therapy at a daily dose of 1.6 µg/kg should be started only after AI has been excluded or treated^{20, 48} Free T4 is the only valuable test (TSH is of no value) for monitoring central hypothyroidism treatment with levothyroxine with the aim to keep fT4 level at the upper quadrant of the normal reference diapason⁴⁸ Patients with fT4 level in this range were found to have lower body weight, BMI and better lipid profile values⁴⁸ Free T4 should be reassessed and the dose of levothyroxine increased by 0.1-0.15 µg/kg in those who also require rhGH and estrogen replacements⁴⁹ Concomitant administration of estrogens and rhGH with T4 necessitates increasing the dose of levothyroxine as rhGH decreases T4 levels and estrogens decreases thyroxine-binding globulin (TBG) level, which increases requirement for levothyroxine^{48,49}

Long-term studies have shown that, patients with a confirmed history of TBI should be aware of the symptomatology suggestive of hypopituitarism.²¹ Garrahy and colleagues found that menstrual disturbances, loss of libido and erectile dysfunction are stronger predictors of hypopituitarism compared to complaints of weight loss and weakness, and suggested to use them as screening criteria for chronic PTHP.³⁷ Treatment of PTHP may improve cognitive function after TBI.¹²

Tanriverdi and colleagues suggested that baseline hormonal assays and dynamic tests after symptomatic TBI of all ranges of severity should be carried out annually for five years and those diagnosed with a deficiency should receive titrated doses of hormone therapy.¹² The management algorithm is summarized in Fig.2:

Prognosis: Generally, the prognosis of PTHP is good. This is because after TBI, hypophyseal revascularization is possible and raised intracranial pressure, edema and decreased perfusion are reversible in nature. Thus, recovery of PTHP is possible within 3 months after TBI in more than 50% of survivors and about three-quarters of cases within a year, with some cases of complete recovery being documented.^{21,50,5} However, in the developed world, about 13-22% of cases of TBI succumb.^{1,51}

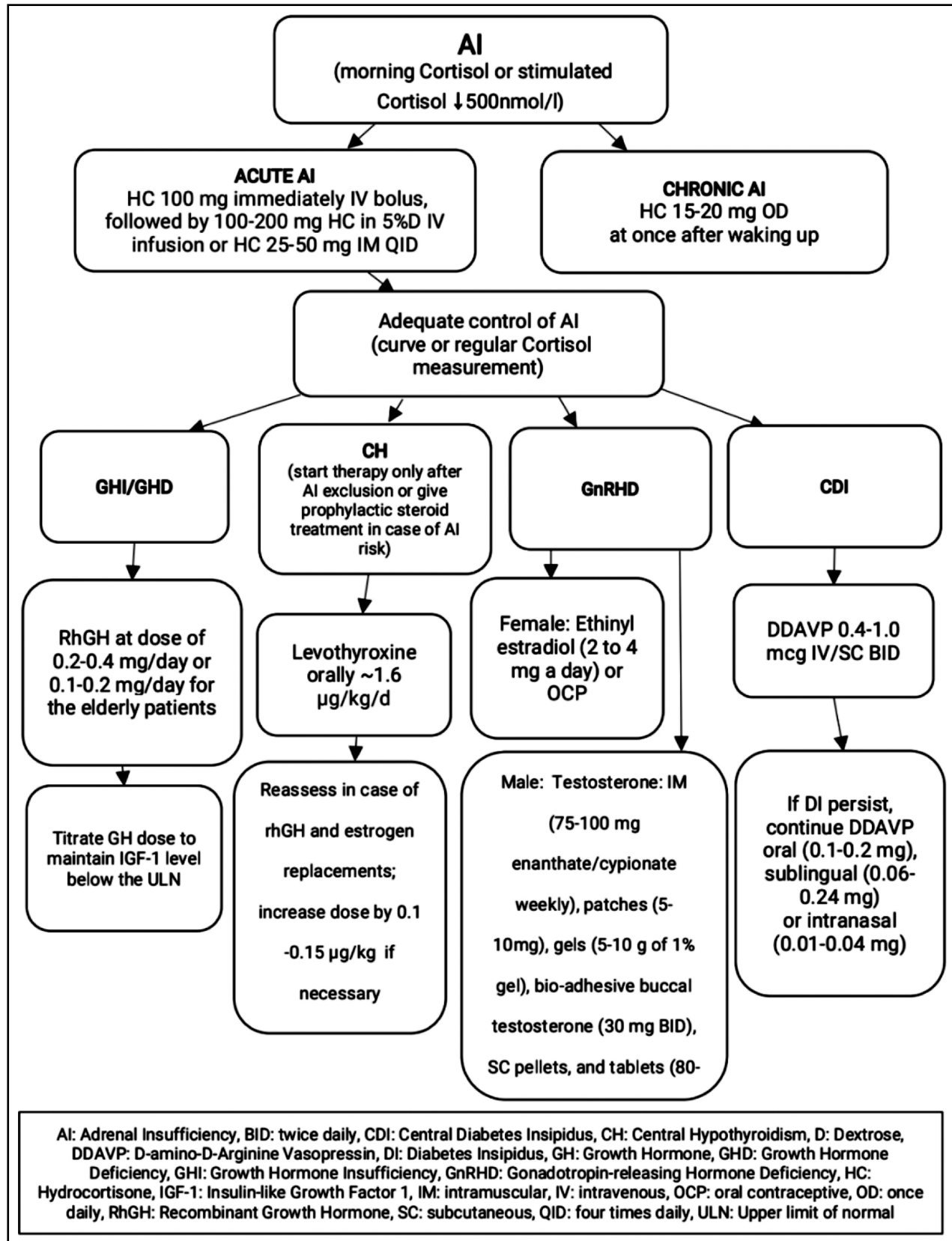
The overall outcome is greatly affected by GH deficiency. Growth hormone plays a role in the stimulation of brain repair following hypoxic injury as well as improving blood circulation in the brain by enhancing vascularity and reduction of vascular resistance. The role of IGF-1 is to stimulate myelination and remyelination while inhibiting the demyelination of the nervous system. Notably, sudden deficiency of growth hormone post TBI impairs preliminary neuroprotection and brain repair.⁵⁰ Presence of GHD is linked to long-lasting adverse medical outcomes. Those with severe GHD have prolonged stay in ICUs.^{17,34} Table-IV summarizes the Prognosis of PTHP.

The exact mechanism for the recovery of PTHP is unclear. Markers, including ubiquitin C-terminal hydrolase-L1, glial fibrillary acidic protein and *α*-II-spectrin breakdown products have been subjected to extensive research before being suggested as novel prognostic markers with subsequent call for change in the pre-existing diagnostic algorithms.²¹

Nevertheless, further studies are required to establish new prognostic markers that will facilitate early diagnosis of patients with the potential of recovery and those with bigger chance of getting chronic hypopituitarism after brain injury. The markers, which are currently under research, are MiRNAs specific antibodies, and specific neuro anti-inflammatory proteins.²¹

CONCLUSION

Frontline physicians in accident and emergency (A&E) departments should maintain a high index of suspicion for post-traumatic hypopituitarism (PTHP), particularly adrenal insufficiency, in the immediate aftermath of head trauma. It is crucial to recognize that hormonal deficiencies during this period may be transient, and new deficiencies can emerge at any stage following the injury. Management requires a multidisciplinary approach involving endocrinologists and neurosurgeons. Hormone replacement therapy remains the cornerstone of treatment, mirroring that of hypopituitarism from other causes. Approximately half of affected patients regain normal pituitary function within one year post-TBI. Prompt identification and appropriate hormonal replacement can be life-saving and significantly improve long-term prognosis and quality of life.

Fig.2: Treatment Algorithm.^{20,21,25,37,38,40,47,48,49}

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Author's Contribution:

All authors contributed in reviewing relevant articles. Volha Tsishutsina drew the algorithms and the tables. Afaf Mustafa Eltyeb Mohammed and Anne Wanjiru Wairagu corrected the spelling and grammar mistakes. Afaf Mustafa Eltyeb Mohammed organized the manuscript according to the guidelines provided by the JPES. In addition, she put the references in Vancouver style and inserted them in text and references list.

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