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Prevalence of pituitary dysfunction in psychiatric patients with mild head injuries

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PREVALENCE OF PITUITARY DYSFUNCTION IN PSYCHIATRIC PATIENTS WITH MILD HEAD INJURIES

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NICHOLAS HEALT

ABSTRACT

Traumatic brain injury (TBI) effects a large number of individuals, both civilians and military personnel, every year. The neuroinflammatory response mounted in the brain following a head injury continues long after the effects of initial subside. While it was initially thought to only occur in moderate or severe TBI, the deleterious effects of this cascade have recently been identified in patients with mild TBI (mTBI). Hypopituitarism is an often underreported condition and can result from TBI of all severity. The long-term sequalae of TBI can manifest in or exacerbate many other comorbidities of brain injury, such as neuroendocrine dysfunction or mental health conditions. Both TBI and hypopituitarism can present with symptoms similar to some psychiatric disorders, or exacerbation comorbid conditions. Veteran patients presenting to their primary care providers with symptoms of irritability, depression, anxiety, or cognitive and behavioral changes may meet criteria to receive diagnoses of psychiatric illnesses prevalent in the military population, while not being evaluated for pituitary dysfunction, and thus receive inadequate treatment. The proposed study aims to identify the prevalence of patients that are receiving psychiatric treatment that have both a history of mTBI and reduced levels of pituitary hormones on serum assays. By identifying a significant portion of this

population, future studies can assess the impact that hormonal replacement has on success of psychotherapy, resolution of symptoms, and impact on functional status, among other factors.

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LIST OF ABBREVIATIONS

ACTH.....Adrenocorticotrophic hormone

BBB.....Blood Brain Barrier

BDI-II.....Beck Depression Inventory-II

BDNF.....Brain-derived Neurotrophic Factor

BUMC-IRB.....Boston University Medical Campus Institutional Review Board

Ca2+.....Calcium

CAPS-5.....Clinician-Administered PTSD Scale for DSM-5

CBT.....Cognitive Behavioral Therapy

CDC.....Centers for Disease Control and Prevention

CDT.....Computed Tomography

CPT.....Cognitive Processing Therapy

CTBIE.....Comprehensive TBI Evaluation

DAI.....Diffuse Axonal Injury

DHEA.....Dehydroepiandrosterone

DoD.....Department of Defense

DSM-5.....International Standards Organization

ED.....Emergency Department

FSH.....Follicle Stimulating Hormone

fT4.....Free Thyroxine

GCS.....Glascow Coma Scale

GH.....Growth Hormone

GHD.....Growth Hormone Deficiency

GWOT.....Global War on Terror

HPA.....Hypothalamic Pituitary Axis

IFN-γ..... Interferon-gamma

IGF-1.....Insulin-like Growth Factor

IL.....Interleukin

K+ ..... Potassium

LH .....Luteinizing Hormone

MDD .....Major Depressive Disorder

Mg2+.....Magnesium

MRI.....Magnetic Resonance Imaging

mTBI.....Mild Traumatic Brain Injury

NGF..... Nerve Growth Factor

NO..... Nitric Oxide

RON .....Reactive Nitrogen Species

ROS.....Reactive Oxidative Species

PCL-5.....PTSD Checklist for DSM-5

PCS ..... Post-Concussion Syndrome

PCP ..... Primary Care Provider

PE.....Prolonged Exposure Therapy

PTHP.....Post Traumatic Hypopituitarism

PTSD.....Post Traumatic Stress Disorder

SI.....Suicidal Ideations

SM.....Service Member

SOCS..... Suppressor of Cytokine Signaling

SSRI..... Selective Serotonin Reuptake Inhibitor

TBI..... Traumatic Brain Injury

TBI-EDHD..... TBI-Related Visits, Hospitalizations, and Deaths

TCRS.....TBI Clinical Reminder Screen

TNF..... Tumor Necrosis Factor

TSH.....Thyroid-Stimulating Hormone

VA.....U.S. Department of Veterans Affairs

VEGF..... Vascular Endothelial Growth Factor

VHA..... Veterans Health Administration

INTRODUCTION

Background

Traumatic brain injury (TBI) is a complicated trauma with a host of far reaching effects on the human body. The majority of these cases in both the general population as well as within the U.S. military are considered mild TBI (mTBI) or concussions.[1] In the past, a mTBI was considered to be self-limiting as the symptoms in most individuals resolve a short time after onset. There are multiple mechanisms of injury that can cause TBI, such as objects striking the head, the head striking a surface or object, rapid acceleration or deceleration, internal structural rotation, and blasts among others. Blast injuries can occur in the general population but are seen more frequently in combat-related populations. And with the ongoing Global War on Terror (GWOT), TBIs due to blasts have become one of the "hallmark" injuries of the operations in Iraq and Afghanistan.[2]

Neuroinflammation is the term used to describe the inflammatory response in the brain following a TBI. This process is initiated with release of cytokines that attract inflammatory markers and activate the central nervous system's microglia. While it is meant to serve as neuroprotection by defending the brain and tissue of surrounding structures, the inflammation develops into a neurodegenerative process as the free radical by-products of this cascade cause damage to neuronal bodies.[3] The continued dysregulation of neuroinflammation may lead to hypoxia, ischemia, and cell death within the tissue. Another detrimental aspect of this process is a disruption of the hormonal pathways of the pituitary, eventually causing hypopituitarism of one or more hormones. If chronic or significant enough, this underrecognized hypopituitarism may manifest with

symptoms of depression, anxiety, and other behavioral changes. While this sequalae of TBI was initially thought to only manifest following moderate or severe TBI, recent research has shown that even mild injuries can lead to persistent neuroinflammation and subsequent hormonal dysfunction.

Individuals that experience a mTBI may choose to not report the injury or seek treatment right away. In fact, most symptoms of mTBI resolve shortly after the injury and do not lead to any further issues. In some individuals however, symptoms persist and often present with persistent headache, dizziness, anxiety, depression, and PTSD.[4] These symptoms may develop immediately or weeks, months, and even years after the injury. Evaluation of a symptomatic TBI typically involves imaging modalities to assess for abnormalities of brain anatomy. In the case of mTBI, these results will usually appear normal.[5] A patient that presents with cognitive and/or behavioral deficits, with normal imaging results, will likely receive a psychiatric diagnosis and ineffective treatment. In some cases, notably in those of military veterans, this leads to worsening of symptoms such as depression, decreased social function, and even suicide.[6]

Statement of the Problem

Neuroendocrine dysfunction secondary to head trauma can be detrimental to the quality of life of a TBI patient. [7] The indolent and insidious nature of this syndrome has led to it being largely underrecognized and unpursued in the clinical setting. When patients seek care for the psychiatric symptoms caused by hormonal dysfunction and endorse a history of TBI, they are assessed for severity of their head injury by clinic evaluation as well as

imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI). With mTBI or a concussion, the initial physical exam and neuroimaging will likely appear normal, and future assessment without new injury is unlikely. These symptoms of depression, anxiety, PTSD, or any of the other cognitive or behavioral sequelae will likely receive a psychiatric diagnosis and be further treated with psychiatric medications and guidelines.

Veterans and military service members (SMs) returning from a combat zone may be predisposed to receiving a psychiatric diagnosis before proper evaluation of pituitary function. Blasts and combat related TBI that are severe in nature may be traumatic enough to cause associated PTSD on their own. However, if an SM with a history of mTBI receives a diagnosis of associated PTSD, they may not undergo the proper work up to evaluate for endocrine function. The result being the same type of psychiatric diagnosis and treatment plan.

If the cause of these psychiatric symptoms is actually due to the dysfunction of the pituitary gland and low levels of neurohormones, these patients are not receiving adequate treatment. Instead, this incomplete or inappropriate treatment may lead to patient frustration with the plan or provider, discontinued therapy, and decreased quality of life.

Hypothesis

Mild TBI can cause neuroinflammation with long-lasting detrimental effects, such as hypopituitarism. Pituitary dysfunction is a treatable cause of many psychiatric complaints

that effects a sizeable portion of patients suffering from mTBI. Identifying the prevalence of pituitary dysfunction among patients given a psychiatric diagnosis will lead to better treatment outcomes.

Objectives and specific aims

The purpose of this study will be to identify the prevalence of pituitary dysfunction in a population of TBI patients that have been diagnosed with a psychiatric condition. Despite continued attention being given to understanding the sequalae of TBI, head injuries of lesser severity remain under-researched. While severe injuries do warrant appropriate attention, the association between mTBI and psychiatric complaints needs more evaluation. By identifying a significant population of individuals suffering from hormonal dysfunction secondary to TBI, this study will help healthcare providers develop better screening techniques and therapies better tailor to patient needs.

- Discuss the epidemiology, pathophysiology, and downstream neuroendocrine effects of TBI.
- Demonstrate a correlation between hypopituitarism and psychiatric symptoms.
- Design a study intended to established the prevalence of pituitary dysfunction in patients being treated for one or a combination of psychiatric illnesses.

REVIEW OF THE LITERATURE

Overview

Traumatic Brain Injury

By definition, a TBI is the result of any type of outside trauma, acceleration and deceleration force, or blast that occurs to the head of an individual that leads to a temporary or permanent change to the brains anatomy, physiology, or biochemistry.[8] There are a variety of classification systems available to categorize TBI. A workshop summarized by Saatman et al. described the five most commonly used systems to define head injury and TBI, which are summarized in the table below (Table 1).[9] The study also highlighted the need for acknowledging special populations, such as those who suffer a TBI from a blast or is young or elderly.

1. Injury severity	Commonly based off of clinical presentation and generally assessed using the Glascow Coma Scale (GCS) to evaluate the patients verbal, motor, and eye-opening responses to stimuli.
2. Pathoanatomic type	A description of where the injury occurred on the patient's body and what brain or surrounding structures are involved.
3. Physical mechanism	A description of how the force of the injury effected the brain.
4. Pathophysiology of injury	The body's response to the insult that occurs at the time of the injury and continues thereafter. This system incorporates an understanding of primary and secondary mechanisms of injury.
5. Evolution of injury cascades	The mechanisms by which the body responds to injury that may further the extent of damage.

Table 1: Head Injury Classification Systems (adapted from Saatman 2008)

Using the Glascow Coma Scale (GCS) to describe the severity of the head injury is one of the most commonly used clinical methods to evaluate the severity of a TBI. As stated above, the patient's response to stimuli is graded individually with scores of 1-4

for eye opening, 1-5 for verbal response, and 1-6 for response to motor stimuli. The cumulative score is assessed with 15 being the best and 3 being the worst. By using the GCS when evaluating a patient with a TBI, the clinician can determine whether the injury is severe (GCS scores of 3-8), moderate (9-12), or mild (13-15).[1] While this technique is widely accepted and implemented, it cannot be applied with high levels of accuracy to individuals who are either injured to an extent of requiring intubation, are intoxicated or incapacitated from drugs or alcohol, young children, or any patient with a previously diagnosed neurological condition. [1] The Department of Defense (DoD) and the Department of Veterans Affairs (VA) have developed a clinical practice guideline to grade the severity of a TBI; assessing GCS (measured at 24 hours after insult), length of post-traumatic amnesia, alterations of consciousness/mental state, length of time of loss of consciousness, and the use of brain imaging to determine whether the TBI was mild, moderate, of severe.[10]

TBI Epidemiology

Throughout 2013, the US saw approximately 2.8 million TBI-related emergency department (ED) visits, hospitalizations and deaths (TBI-EDHDs). Of these ED visits, approximately 282,000 patients were hospitalized and approximately 56,000 patients died due to TBI-related conditions. Higher rates of TBI-EDHDs were seen in males compared to females, with the highest rates seen in patients 75 years of age or older. Falls, being struck with or against an object, and motor vehicle accidents (MVAs) were among the leading mechanisms of injury.[11] ED visits due to TBI increased overall from 2007 to

2013, from 534 per 100,000 to 787 per 100,000.[11] The increase could reflect an overall increase in the amount of TBIs occurring or be due to better reporting caused by higher public awareness to the consequences of head trauma. It is important to acknowledge that these statistics are likely underestimates, especially for mild injuries. Individuals are likely not to seek care if they sustain a mild TBI or a concussion. In one survey of collegiate athletes, approximately 43% of the survey populations reported that they had willingly chose to not seek care despite experiencing concussion symptoms.[12]

Considered as one of the hallmark injuries of the Global War on Terror (GWOT) and its operations in Iraq and Afghanistan, TBIs have warranted increased surveillance in the U.S. military.[13] In a report to the US Congress, the Centers for Disease Control and Prevention (CDC) along with the National Institutes of Health (NIH) stated that 235,046 SMs from the Army, Air Force, Navy, and Marine Corps were diagnosed with a TBI from 2000-2011. This is 4.2% of the total number of SMs in each of those components of the military (5,603,720). The majority of these SMs, 76.6%, were diagnosed with a mTBI, with an overall increase in the rate of mTBI from 2000 to 2011. The report also states that the overall rate of TBI among active duty SMs increased from 720.3 per 100,000 to 1,811.4 per 100,000.[2]

TBI Pathophysiology

The majority of our understanding of TBI pathogenesis comes from the research of moderate-severe injuries. The current understanding of TBI pathophysiology consists of a primary and secondary mechanism, often occurring concomitantly. The primary

mechanism of injury occurs immediately and is due to the effects of the mechanical force of the insult, such as rapid acceleration or deceleration, blunt or penetrating trauma, or blast waves, on the brain tissue or surrounding structures. Secondary injury is a progression of several complex, cascading processes that are triggered by both direct injury to the brain, and also as a result of conditions occurring elsewhere in the body (edema, impairments to blood flow or oxygen, infections, etc.).[14] Both primary and secondary mechanisms can lead to either diffuse or focal injury, and both can occur together in a single head injury. Diffuse injuries are commonly seen in non-contact, rotational injuries while focal injuries are more consistent with a force making contact to the head.[15]

The physical force of a primary injury can lead to subsequent diffuse axonal injury, vascular tears, focal cortical contusions, edema, and/or intracranial hemorrhages. Diffuse axonal injury (DAI), considered the best example of a primary diffuse TBI, most commonly affects the white matter tracts of the brainstem, corpus callosum, basal ganglia, thalamus, and the cerebral hemispheres.[14] Shortly following a DAI, the membranes of the affected neuronal axons see a large influx of calcium (Ca^{2+}), and can appear visually swollen within minutes and can continue for 24-48 hours. The influx of calcium causes activation of proteolytic pathways that target the components of the neuronal cytoskeleton, causing further distortion and interruption of the neurons signaling ability.[14] In addition to activation of axonal proteolysis, the calcium imbalance causes mitochondrial swelling/injury, which can induce activation of apoptotic pathways mediated by caspase. Increasing levels of Ca^{2+} within the axon have been observed to

cause cytoskeleton breakdown as late as 24 hours post injury.[16] Over time, some of these axons will remain intact while others will undergo axotomy or Wallerian degeneration.[17] The cascading effects of increased calcium show how DAIs can be classified as both a primary and secondary injury. The more severe DAIs are associated with immediate loss of consciousness and comas, while the more milder forms are typically reversible concussive injuries.[15]

The cellular effects of focal injuries are typically limited to the site of impact and the surrounding tissue, such as cortical contusions and both intra- and extracerebral hemorrhage. These injuries are commonly seen in rapid deceleration injuries as well as traumas caused by objects striking a stationary head.[14] Focal cortical contusion injuries are typically caused by shearing forces that damage the cerebral vasculature, causing an intracerebral hemorrhage. This can lead to edema, hemorrhages, ischemia, and death, depending on extent of the injury and secondary mechanisms.[14]

Secondary injury is a progression of several complex, cascading processes that are triggered by both direct injury to the brain, and also as a result of conditions occurring elsewhere in the body (impairments to blood flow or oxygen, infections, etc.). In cases of severe TBI, these cellular changes lead to damage via further downstream mechanisms. There are four currently defined secondary mechanisms for severe TBI: (1)activation of apoptotic pathways, energy failure, ischemia, and excitotoxicity; (2)secondary increased intracranial pressure and swelling; (3)axonal injury; and (4)inflammation and regeneration.[18] Secondary injury occurs immediately at the onset of the insult, starting with rapid ionic fluctuations and release of neurotransmitters and can continue for months

post-injury. As discussed previously, the stretching of neuronal axons caused alterations in the neuron's membrane. The resulting ionic instability, chiefly the unintended opening of voltage-gated potassium (K^+) channels, leads to neuronal depolarization and excessive releases of excitatory glutamate. If severe enough, this action acts as a positive feedback loop, resulting in increased glucose needs from the brain's attempt at homeostasis and subsequent increased lactate production.[16] Accumulation of lactate can lead to acidosis, membrane damage, membrane damage, alterations in blood brain barrier permeability, and cerebral edema.[19] The excess of glutamate is also the basis for excitotoxicity, a secondary mechanism of cell death, leads to the overstimulation of neuronal receptors in the synaptic space. The continued activation of these receptors causes an influx of sodium (Na^+) and Ca^{2+} into the cell.[20] In addition to the effects of increased Ca^{2+} already discussed, intracellular increases can lead to the activation of apoptotic and necrotic pathways, resulting in cell death.[20] Secondary cell death can also be triggered by oxidative stress. As a result of these complex secondary injury pathways, a build-up of reactive oxidative species (ROS) and reactive nitrogen species (RON) occurs. The combination of excessive ROS/RON with the brain's impaired antioxidant ability results in damage to multiple structures and organelles, in turn leading to more neuronal cell death.[21,22] If severe enough, secondary injury following TBI can also lead to a mechanical disruption in the blood brain barrier(BBB). As the tight junctions of the BBB are damaged, it loses its highly selective permeability. This allows an influx of blood and immune factors, exacerbating the oxidative stress, cell death, and inflammation. If the

inflammatory response becomes too great, it can lead to increase intracranial pressure (ICP) and ischemia.[23,24]

Neuroinflammation

The neuro-inflammatory response caused by a TBI is initiated to provide neuroprotection and to defend the site of injury from any possible invading pathogens. The microglia, along with astrocytes, represent the bulk of the central nervous system innate immune system and are the hallmark of the neuroinflammatory response.[25,26] In an uninjured adult brain, microglia are responsible for the removal of apoptotic cellular debris via phagocytic properties, trigger further activation of glial cells, release of pro-inflammatory cytokines, and express neurotrophic factors. When an individual experience a TBI, the microglial response is considered a "double-edge sword".[3] In the early stages of a TBI, the response of the microglia is intended to provide neuroprotective benefit by upregulating neurotrophic factors (BDNF, NGF, VEGF) and pro-inflammatory cytokines. When activated, microglia polarize into "classical" M1 and "alternatively activated" M2 subtypes. The M1 subtype secretes high levels of the proinflammatory cytokines: interferon-gamma (IFN-γ), tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-12, and low levels of IL-10. After being secreted, the cytokines IL-1-β and TNF-α go on to increase inducible nitric synthase and act as inducers of apoptosis in both animal and human studies.[3] When in the M2 configuration, microglia act in a more anti-inflammatory manner by secreting high amounts of IL-10 and transforming growth factor (TGF)-β, and suppressor of cytokine signaling (SOCS) and much lower levels of TNF-α,

IL-1, IL-12 than their M1 counterparts. These M2 microglia are also responsible for clearance of cellular debris and are considered to function in a neuroprotective role. Some therapeutic strategies have been aimed at inducing release of these pro-survival, anti-inflammatory, cytokines. Each subtype will also continue to propagate further polarization of microglia into that subtype.[3]

As the cytokines continue to be upregulated, the response becomes more neurodegenerative with the downregulation of neurotrophic factors and upregulation of the pro-death cytokines TNF-alpha, IL-1b, and IL-6. Microglia also release neurotoxic products such as ROS, RON, and nitric oxide (NO), contributing to further damage by oxidative stress.[3,26]

After a TBI, the microglia can remain activated for weeks and even years in some cases.[27] A study examining the inflammatory response following moderate to severe TBI conducted by Ramlackhansingh et al showed continued microglial activation as late as 17 years after initial injury. This suggests a long-term, and possibly chronic, inflammatory response to TBI.[28] Chronic neuroinflammation has been suspected as being one of the common neuropathologic mechanisms of some psychiatric disorders, such as major depressive disorder, bipolar disorder, and schizophrenia.[29]

One mechanism of TBI that is somewhat unique to the military populations is blast injuries. Blasts can cause bodily injury by several mechanisms. Explosive blasts produce rapid pressure transients that travel faster than the speed of sound, causing primary injury. This rapid over-pressure most commonly effects hollow organs.[13,30] Secondary injury occurs when objects or debris, such as shrapnel, put into motion by the

blast strikes the body. This can cause direct trauma where ever contact is made, and is often the cause of an identifiable TBI. Tertiary injury occurs when the blast displaces an individual, causing them to contact another surface. Quaternary injuries result from other insults such as toxic inhalation, radiation, or other mechanisms set in motion by the blast.[13,18,31] Injury to the brain from the primary blast is thought to occur via direct transcranial propagation, propagation through the vascular system, or by traveling in the cerebral spinal fluid along the spinal cord to the brain stem.[32] The shock wave created by the explosion may also create multiple "micro-cavitations" that form and pop rapidly, damaging surrounding tissue and triggering secondary injury mechanisms. Since these rapid changes resolve quickly and do not lead to lasting damage, neuroimaging studies appear normal. This mechanism of injury may occur in patients with mild blast induced TBI or those with polytrauma, making clinical assessment of neurological status challenging.[33]

Severity of TBI caused by blasts is similar to TBIs caused by other mechanisms and can result in the same physical, neurological, behavioral, and emotional manifestations. In severe injuries, edema, DAI, and hemorrhage have been observed; with edema occurring sooner and cerebral vasospasm present in a significant number of patients.[32,34] Mild TBIs caused by blasts have been called "blast concussions", with reported symptoms such as brief retrograde amnesia, headache and confusion, difficulty concentrating, sleep disturbances, and anxiety.[35]

TBI Clinical Presentation

Clinically, a patient suffering from a TBI may present with a wide array of symptoms. As discussed above; severe injuries often present with a patient who may be unresponsive or displaying obvious motor and/or verbal deficits. Apart from those instances of severe injury however, clinical presentation of a mild to moderate TBI varies widely and may include physical, cognitive, and even behavioral manifestations. Physical signs and symptoms include: headache, nausea, vomiting, dizziness, blurred vision, weakness or paralysis, loss of sensation, spasticity, speech and swallow difficulties, coordination and balance impairment, and even new onset of seizure activity. Cognitive changes from TBI can range from attention, memory, and concentration deficits to impairment of executive control, judgement, and abstract thinking.[2] Patients may also experience behavioral changes following a TBI. With a moderate or severe injury, major depression is reported in an alarming 25-40% of cases.[36] Other behavioral sequalae include: anxiety, agitation, irritability, aggression and violence, impaired self-control, impaired self-awareness, and alcohol or drug abuse/addiction among many other behavioral changes following a TBI. Changes to sleep behavior and other neuropsychiatric afflictions have also been noted.[2]

TBI Screening

Currently, all GWOT veterans complete the TBI Clinical Reminder Screen (TCRS) upon enrollment at their Veteran Affair Medical Center. The initial screening is typically conducted by the veteran's primary care provider (PCP).[10,37] Veterans that

screen positive for TBI are then offered a more comprehensive evaluation, called the Comprehensive TBI Evaluation (CTBIE) in order to better assess the injury and coordinate more focused treatment with specialists, notably the Spinal Cord Injury and Disorders team.[37,38]

Mild TBI

As stated above, mild head injuries account for the majority of reported TBI cases. Concussion is considered a mTBI, though it is sometimes used clinically to describe an injury that results in some level of altered consciousness and is usually reserved for an injury received during a sporting event. For the basis of this review, terms mTBI, concussion, and mild head injury are considered clinically synonymous with one another.[39] As a result of the increased attention to TBI, the U.S. military implemented more aggressive screening measures for mTBI in 2006. This likely caused the dramatic increase in incidents that was included in the report to congress.[2,40]

While the pathophysiology of mTBI and concussions is not entirely known, it is apparent that these injuries are a part of a disease process different from that of the moderate-severe TBIs. Two important processes that are known to be involved with mTBI are a specific pathway during axonal injury and deficits of working memory.[41] In one animal study, traumatic axonal injury was seen up to 3 days after concussion and degenerating axons were seen at 14 days.

What constitutes as a mTBI varies in clinical practice. As outlined above; a mTBI is considered in any head injury that results in a loss or alteration in consciousness for 30

minutes or less, confusion or disorientation and/or memory loss for less than 24 hours, normal neuroimaging, and a GCS of 13-15. Headache is the most reported symptom following mTBI. Others include dizziness, nausea, fatigue, lethargy, and changes in sleep pattern. The cognitive deficits due to TBI are characterized by impaired attention, memory, and/or executive function and may cause the patient to become irritable, anxious, or depressed. These cognitive deficits that may result from TBI generally resolve within days in the case of a mTBI. In the majority of mTBI cases, these symptoms resolve without issue shortly after the injury. However, when a patient still experiences any or a combination of these symptoms, it is considered post-concussion syndrome (PCS).[41,42] Depression is commonly reported in those whose symptoms do not resolve. Individuals with mTBI and subsequent depression have also shown to have associated increased anger and aggression, as well as a higher risk of self-harm and suicide.[4]

Neuroendocrine Dysfunction

Neuroendocrine dysfunction has been identified as an associated sequela of TBI since the first case of post-TBI hypopituitarism (PTHP) was diagnosed in 1918. Neuroendocrine refers to the communication between the nervous system, hypothalamus, and pituitary gland. The pituitary gland secretes multiple hormones in response to various stimuli. Pituitary hormones have multiple effects on cognitive ability and given that TBI patients can have a very non-specific presentation, PTHP is considered to be underdiagnosed. However, a systemic review conducted in 2007 by Schneider, et al

concluded with a pooled prevalence of 27.5% of subjects for in the chronic phase of a TBI displaying hypopituitarism.[43,44]

The pituitary gland is encased in the sella turcica, bony depression of the sphenoid bone, and is composed to two anatomically and functionally distinct organs of the endocrine system, the anterior and posterior lobes. These lobes are connected to the hypothalamus by the pituitary stalk, which contains nerve fibers and portal vessels used in the regulation of hypothalamic and pituitary hormones. The posterior lobe is an outgrowth of the hypothalamus that stores and releases oxytocin and vasopressin. Neither of the two posterior pituitary hormones have been implicated in neuropsychiatric conditions, and will not be discussed here. The larger and more glandular anterior lobe is responsible for production of several secretory hormones, which are regulated by inhibiting and releasing hormones of the hypothalamus.[45]

Each anterior pituitary hormone is secreted by a specific pituitary cell and each set of cells are distinctly located within the anterior pituitary. The cells that secrete growth hormone (GH), called somatotrophs, constitute the majority of pituitary cells at 40%. The corticotrophs producing adrenocorticotropic hormone (ACTH) represent 20%, lactotrophs secreting prolactin comprise between 15-25%, gonadotrophs that secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH) constitute 10-15%, and the TSH secreting thyrotrophs make up 5%.[45]

Determining the extent of hormonal dysfunction involved in PTHP is based on identifying the number of hormonal pathways involved. Deficiency of GH is the most commonly reported in moderate to severe TBI, with a prevalence of 2-66%. Deficiencies

of the other hormones were reported with wide ranges as well; with adrenal deficiency ranging 0-60%, hypothyroidism and central hypogonadism ranging from 0 to 29%, and hyperprolactinemia from 0 to 48%.[43,46]

While pathophysiology of PTHP is not thoroughly understood, both the primary injury as well as the secondary mechanisms of TBI are implicated. Mechanical trauma may cause fractures in the sphenoid bone and sella turcica, leading to damage of the hypothalamus, pituitary stalk, and/or lobes of the pituitary gland. Rotational and shearing injuries to the stalk itself causing partial or complete transection and/or hemorrhage into the sella turcica, with subsequent infarction of pituitary tissue, has been observed in patients post moderate to severe TBI.[47,48] Infarction or ischemia of the pituitary due to primary and secondary injury is highly suspected to be a root cause of PTHP. Evidence of anterior pituitary infarction was published as early as 1959. In those cases, rupture of the pituitary stalk following head trauma was found during autopsy.[49] The blood supply to the pituitary gland is tenuous and trauma to the hypophyseal portal veins has been identified following TBI. Ischemia may also occur due to the secondary mechanisms discussed above, that result in hypotension, hypoxia, anemia, and cerebral edema.[47,50,51]

Since a TBI can cause damage to any part of hypothalamus, pituitary stalk, or gland; the clinical manifestations of a patient with secondary neuroendocrine dysfunction can range greatly.[43,45] Growth hormone is involved in cellular processes such as synthesis and release of insulin-like growth factor (IGF-1), microtubular regeneration, lipid metabolism, and the dendritic growth and regrowth of neurons. The effects of GH are both direct and indirect, with IGF-1 acting as a mediator. As such, decreased IGF-1 levels

cause disruption in lipid and microtubule metabolism, leading to impaired neuronal, somatic, and dendritic growth.[43,45] A patient with growth hormone deficiency (GHD) can present with fatigue, poor memory and concentration, depression, anxiety, along with reduced exercise performance, and increased body fat.[45] When compared to TBI patients with normal steroid levels, TBI patients with GHD were seen to have higher disability scores, greater depression and fatigue, and worse emotional well-being.[52]

The communication between the hypothalamus, pituitary, and adrenal cortex is known as the hypothalamic pituitary adrenal (HPA) axis. The adrenal cortex responds to the ACTH released from the pituitary gland with production of several steroids; mineralocorticoids, glucocorticoids, and adrenal androgens. Steroids produced in this process, such as cortisol, are major components of the body's stress response.[45] Deficiencies in ACTH and cortisol can manifest as fatigue, weakness, and impairment to the physiological stress response. Acutely, a deficiency of ACTH can be deadly. A benefit of this is that is usually readily identified during the initial assessment and treatment of an injury.[45] In cases of chronic cortisol deficiency, mood disorders, decreased memory, and frank psychosis have been seen.[43] A positive correlation between levels of cortisol and GCS, with the development of anxiety, has been observed in severe TBIs.[53] Once stimulated by ACTH, the adrenal cortex also releases a sex-steroid precursor known as dehydroepiandrosterone (DHEA) and the sulfate ester of DHEA, DHEA-S. Both DHEA and DHEA-S are also synthesized in the brain and have shown neuroprotective effects by regulating activation of microglia during an inflammatory response.[54]

Thyroid hormones are released in response to TSH from the pituitary. The TSH is secreted following release of thyrotropin-releasing hormone from the hypothalamus. Dysfunction within the thyroid axis has been shown to mimic that of TBI induced neuroendocrine deficits. Hypothyroidism may present with impaired information processing, executive function, and aspects of memory.[45,55] Clinical and subclinical hypothyroidism has also been described as a risk factor for depression.[56]

The follicle stimulating hormone (FSH) and luteinizing hormone (LH) released by the gonadotrophic anterior pituitary cells are responsible for the regulation of gonadal steroid hormone synthesis. Deficiency of these hormones, testosterone and estrogen, have a multitude of effects on the body. Deficient males have decreased libido and fertility, decreased muscle mass, muscle weakness, and even loss of secondary sexual characteristics. Females with low estrogen also suffer from decreased libido and fertility, as well as secondary amenorrhea and decreased bone density. Estrogen and another gonadal steroid hormone, progesterone, have been recently identified as being neuroprotective following TBI. The mechanism for neuroprotection is not exactly known, the hormones' effects on microglia and astrocytes, modulation of the inflammatory response, and mediation of excitotoxicity are thought to be involved. When administered in the acute phase of moderate to severe TBI, progesterone lead to a decreased mortality rate and improved neurological outcome in patients of severe TBI.[57,58]

With an exception given to ACTH, and occasionally TSH deficiency, diagnosis of PTHP acutely after injury is difficult due to the variety of physiologic responses triggered by either the primary injury or medications given as part of the treatment. In order to

accurately identify a hormonal deficiency, each hormone requires individual testing.[59] Normal values for each hormone are summarized in the table below, levels confirmed to be below normal are considered diagnostic of deficiency. For assessment of ACTH deficiency, serum cortisol levels are tested between 8-9 am. When findings are deemed "indeterminate", a corticotropin simulation test is performed to confirm or rule-out the diagnosis. Thyroid hormone function is tested by measuring levels of serum free-dT4 (fT4) and TSH, with deficiency being diagnosed when fT4 levels are below normal and TSH levels are low, normal or slightly elevated.[60] Gonadotropin function is tested differently based on patient's sex. To diagnose GHD in males, determined by measuring serum levels of IGF-1. This test is considered insensitive however, and in the absence of other hormonal deficiencies, provocative tests designed to stimulate GH response are used.[60,61] Gonadotropin deficiency in males is identified by measuring serum testosterone, LH, and FSH.

Hormone	Normal range	Units
Free T_3	1.6-3.8	pg/ml
FreeT_4	0.89-1.7	ng/dl
TSH	0.17-4.05	μIU/ml
Basal cortisol (8 A.M.)	9.4-26	μg/dl
FSH		
Male	2.2-10	IU/L
Female	3.4-12	IU/L
LH		
Male	1.8-8.4	IU/L
Female	3-18.6	IU/L
Testosterone		
Male	3-12	ng/ml
Estradiol (E2)		
Female	57-227	pg/ml

TSH: Thyroid stimulating hormone, FSH: Follicle stimulating hormone, LH: Luteinizing hormone

Figure 1: Pituitary Hormone Normal Values (Accessed from Google Images)

Psychiatric Manifestations

The association between combat-related TBI and behavioral changes is not a new discovery. Reports from World War I describe individuals who survived intense and excessive artillery shelling as showing severe anxiety and distress, with some even developing sudden blindness, muteness, or catatonic states. As of 2009, of the 327,388 veterans from the GWOT using VHA services, nearly 90% of patients who had received a TBI diagnosis were also diagnosed with a psychiatric condition. The most prevalent comorbid condition was PTSD, occurring in 73% of TBI patients. Depression and anxiety were the second and third most common diagnoses, respectively.[62]

The VA and DoD's definition of PTSD describes a condition of persistent symptoms and associated functional impairment following exposure to an event or

situation that threatened serious injury or death.[63] Studies estimating the prevalence of PTSD in veterans of the GWOT show some variability. According to the VA, since the beginning of Operations Iraqi Freedom and Enduring Freedom, it is estimated that between 11-20% of deployed service members have or will have PTSD in any given year.[64] A study analyzing 60,000 GWOT veterans identified 13.5% of both deployed and non-deployed SMs had a positive screening for PTSD, while other rates have been higher at 20-30%.[6,65] Depression, the most common comorbid psychiatric condition with PTSD, is prevalent in as high as 25% of veterans seeking treatment at VA medical centers. There are several disorders that can cause a diagnosis of depression, though major depressive disorder (MDD) is the most commonly diagnosed in veteran populations.[66]

The pathophysiology of PTSD is largely unknown. Imagining studies using MRI have shown diminished volume of the anterior cingulate cortex, left amygdala, and hippocampus in patients diagnosed with PTSD.[67,68] Patients have also displayed increased noradrenergic activity with increased levels of norepinephrine concentrations in their CSF.[69]

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) dictates the various criteria used to diagnose PTSD and depression, as well as all other psychiatric conditions.[70] The criteria listed in DSM-5 for each disorder is also what most screening tools are derived from. The current gold standard for assessment of PTSD in both veterans and civilians is the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). This technique involves a 30-item interview that takes 30-60 minutes to complete. Other methods include the PTSD Checklist for DSM-5 (PCL-5) and the Mississippi Scale

for Combat-Related PTSD, both being self-reported questionnaires.[71] The VA/DoD clinical guidelines based off of the DSM-5 require exposure to a traumatic event as either directly to the individual, witness by the individual as it occurs to others, learning that a traumatic event occurred to a loved one or family member, and/or experiencing repeated or extreme exposure to aversive details of the event.[70] For diagnosing depression, patients must identify key symptoms (displayed in Table 2), and be functional impaired by 5 or more of the any symptom for nearly every day throughout a 2 week period.[70] The Beck Depression Inventory-II (BDI-II) is a 21 item questionnaire that is used to evaluate depressive symptoms and score them on a scale ranging from no depression to severe depressive symptoms.[66]

Symptoms of PTSD may manifest from weeks to years following a traumatic experience. A study of SMs hospitalized after a serious combat injury showed that the majority of its study population displaying symptoms of either PTSD or depression at 7 months after the trauma did not have those symptoms at one month after.[72] Depression can manifest acutely or chronically over years. The disease course tends to be much more unpredictable and can even recur throughout a patient's lifetime.[73]

Major Depression Disorder Symptoms
1. Depressed mood 2. Anhedonia 3. Feelings of worthlessness or guilt 4. Suicidal ideation, plan, or attempt 5. Fatigue or loss of energy 6. Sleep disturbance (increased or decreased) 7. Weight or appetite disturbance (increased or decreased) 8. Decreased ability to think or concentrate, or indecisiveness 9. Psychomotor retardation or agitation

Table 2: Symptoms of Major Depressive Disorder

Management of these psychiatric conditions involves both psychological and pharmacological approaches, sometimes in combination, depending on the condition and its severity. For PTSD, cognitive behavioral therapy (CBT) is considered the first-line treatment. In the VA/DoD guidelines for management of Post-Traumatic Stress, CBT involves either cognitive processing therapy (CPT), prolonged exposure (PE) therapy, or a combination of the two.[63,71] In CPT, a therapist works with the patient to identify that individual's negative thoughts associated with the traumatic event, working together to develop coping mechanisms. PE therapy involves using the safety of the clinical setting to revisit the traumatic event as a means for the patient to change their reaction and find mechanisms to deal with the fear or stress they experience.[71] When psychotherapy is not sufficient to treat PTSD, or if therapy is not a viable option, pharmacotherapy using selective serotonin reuptake inhibitors (SSRIs) is the next option. While SSRIs have been shown to be effective in the treatment of PTSD, psychotherapy is preferred and has demonstrated more effective results.[71,74] SSRIs are also used as the first-line treatment for MDD and other depressive conditions.

Both CPT and PE have been shown to be highly effective in treatment of PTSD. Despite this however, many patients report no meaningful change in symptom and retain their diagnosis.[75] Treatment drop-out rates can be high as well, especially within the military and veteran populations. Early discontinuation of treatment can near 24% of veterans undergoing CBT, with reported reasons that include ineffective treatments, discomfort with their mental health provider, and stigma among others.[75,76]

Patients with either PTSD, MDD, TBI, or any combination of the three are also at higher risk of experiencing suicidal ideations (SI) and suicide attempts. The GWOT brought attention to the association of PTSD and suicide, with multiple studies showing veterans of military operations in Iraq and Afghanistan being more likely to receive a PTSD, MDD, or other anxiety diagnosis and being at a higher risk of suicide.[77,78] When controlled for PTSD and MDD, veterans with mTBI, especially those with more severe memory deficits, are also at an elevated risk of suicide.[79] In fact, even in the absence of suicide, death rates of veterans with at least one mental health condition (including depression, PTSD, and anxiety) are much higher when compared to the general population.[80]

Existing research

A recurring theme regarding TBI is that the majority of research has been focused on moderate to severe injuries. In recent years however, the significance of mTBI and blast TBI has led to increasing attention being placed on better understanding the

presence and implication of neuroinflammation of mild injuries as well as long-term sequelae.

As previously discussed, mTBI was initially thought to be a transient injury that resolved without long-term pathology. A scoping review conducted by McInnes et al. analyzed data from 45 studies of mTBI cases and assessed the impact of a single mTBI on short- and long-term cognitive function.[81]

The cognitive domains assessed for impairment included: executive function, learning/memory, attention, processing speed, and language function. Of the 3593 participants with single mTBI included in the reviewed articles, approximately 55% displayed cognitive impairment at >3 months post-injury.[10,64] After McInnes et al. removed articles that did not explicitly state that their subjects had only a single mTBI, the portion of the remaining population with cognitive impairment was still 55%. In comparing their result to the previously reported ~15% of mTBI patients suffering from PCS, McInnes et al. identified several possible reasons for the gap. For example, the studies at resulted in 15% may have used diagnostic methods that were not capable of assessing for subtle cognitive impairment. In fact, the many differing approaches to evaluating and diagnosing both mTBI and its potential sequelae has been a major limitation to gaining more definitive insight on the chronic effects of mTBI through literature reviews.[81]

There are many other limitations noted in this study; lack of longitudinal studies available for review, excluding studies that did not have full texts accompanying their abstracts, including studies with differing methods of assessing outcome measures, and

not creating subgroups of participants based on symptom or mechanism of injury to name a few. Despite these limitations and any others, this review provides strong support to the theory that one mTBI causes long-term detrimental impacts on brain function.

In 2017, Radtke et al. conducted a review of neuroinflammation and its role in certain psychiatric conditions. The review highlights evidence of elevated cytokines, both pro-inflammatory and anti-inflammatory, in blood samples of patients with depression, anxiety, and PTSD among other psychiatric disorders.[82] Some patients with a viral CNS infection presented with increased aggressiveness and portions of that same patient group continued to show aggressiveness as well as memory disorders as long as one year after their initial hospitalization. Despite the many different factors involved with comparing CNS infection and brain injury, it is important to note that both can trigger inflammatory responses and the development of memory, mood, or behavioral disorders is seen in both populations.[82] Evidence of microglial pathology was identified in postmortem studies and PET imaging in patients with depression. In some animal studies reviewed by Radtke, reduced levels of microglia were found in rodents with stress-induced depression. Microglia activation along with a proinflammatory cytokine response was observed in rodents with associated cognitive and behavioral deficits.[82]

While the elevated cytokine profiles in the periphery support the neuroinflammation having a role in these disorders, being able to assess these levels directly in brain tissue following TBI would better established an association for those with post-TBI psychiatric disorders. The study does not delve into the demographics of

the patients, so being able to tie these results to those with post-TBI psychiatric symptoms would require further analysis or testing.

Improvements in fatigue, mood, and neuropsychological state were recently assessed in a clinical trial studying growth hormone (GH) replacement in symptomatic subjects with a history of mTBI.[83] A small number of subjects, 7 males and 12 females, met the inclusion criteria of being at least 6 months post mTBI-injury, with mTBI defined in the study as having less than 30 minutes of loss of consciousness, disorientation, confusion, or loss of memory, and meeting 3 or more criteria in the Brief Fatigue Inventory questionnaire. GH secretion was assessed using a glucagon stimulation test and included subjects were found to be either deficient (<3 mg/dL), or insufficient (<8 mg/dL). Subjects were randomly assigned to receive either recombinant human GH first (GH during months 1-3, placebo during months 4-6, GH months 7-12) or placebo first (placebo months 1-3, GH months 4-6, GH months 7-12).[83] Assessment of IGF-1 in serum was obtained via blood testing at months 1, 3, 4, 6, and 12. At baseline and at months 3, 6, and 12, fatigue, mood, and neuropsychological (to include depression, verbal learning, verbal fluency, and visuospatial memory) testing was conducted along with additional assessments and neuroimaging (MRIs). At 12 months, fatigue scores decreased from 36.8 to 14.6 ($p=0.002$), and subtest scores of tension/anxiety decreased to 4.8 from 11.0 ($p=0.036$). While other assessments did not show clinically significant improvements, neuropsychological examinations did suggest a decrease in symptoms of depression. Weaknesses of this study include the small sample size and sample population (predominantly female). This study does bring attention to both the association of PTHP

following mTBI, and the symptomatic improvement following hormonal replacement therapy.[83]

Although there are multiple associations between mTBI, development of pituitary dysfunction, and symptoms of PTSD and depression, there have been no formal studies evaluating the prevalence of hypopituitarism in patients receiving psychiatric treatment at VA medical centers. As evidenced by the multifactorial nature of developing any one of these conditions, a host of causes can lead to an individual being diagnosed with a psychiatric condition. Despite years of research indicating the significant prevalence of mTBI-induced PTHP, no formal guidelines exist within the VHA to assess an individual's neurohormonal level as part of the work up in diagnosing either PTSD or MDD.

METHODS

Study design

For this study, researchers will use a one-group, cross-sectional study establishing the prevalence of hypopituitarism among SMs with a clinical diagnosis of PTSD with and without a history of mTBI. Participants found to have pituitary dysfunction by serum testing will then further stratified into subgroups assessing etiology of mTBI (blunt trauma, fall, blast, etc.), timing from initial injury, and symptom severity following treatment.

Study population and sampling

The study population will be composed of veterans that have separated or retired from military service and have received clinical diagnoses of PTSD (as defined by the DSM-V criteria) as well as mTBI (self-reported or as defined by the VA Clinical Practice Guideline). For this study, the population will be composed exclusively of males receiving their primary psychological care through the VA Healthcare System.
Given the TBI pathophysiologic differences between males and females described above, as well as the disproportionately low number of female patients within the VA, females will be excluded from the study to reduce the number of variables. As hypopituitarism is seen in older, otherwise healthy patients, older age may confound study results as well. This will be mitigated by limiting the age of participants to 70 years or younger. All other

inclusion and exclusion criteria are listed in Table 3. Criteria for mTBI will be assessed using the VA/DoD guidelines, while PTSD and depression will be evaluated using the CAPS-5 and BDI-II, respectively.

Inclusion Criteria	Exclusion Criteria
• Male veteran patients with a history of at least one mTBI, defined by the VA/DoD guidelines • Meeting criteria for, or receiving psychiatric care for diagnosed PTSD, MDD, or anxiety (defined by DSM-5) • Care must come primarily from VHA providers, with records accessible through the VA EMR. • Age less than 70 years	• History of moderate-severe TBI, TBI with LOC greater than 30 minutes, or history of penetrating head wound • History of seizure disorder • History insulin-dependent diabetes • Current or past diagnosis of schizophrenia, bipolar disorder, any disorder with psychotic features, or dementia (all defined by the DSM-5) • Documented pituitary disorder with confirmed etiology

Table 3: Inclusion/Exclusion Criteria

As discussed in the above literature review, the known prevalence of hypopituitarism following mTBI varies greatly (up to 27.5% of one review), with no known study assessing pituitary dysfunction in psychiatric patients.[44] Since there is no known established a known prevalence in this population, the proposed study will be designed with an estimation of approximately 12.5% of psych patients having concomitant mTBI -induced pituitary function is (P=0.125). To maintain a confidence interval of 95%, this study will need to recruit a minimum of 712 subjects. In an attempt

to mitigate a drop in confidence interval, the target sample size will be set at 791 (N=791), which will account for an estimated 10% of subjects being lost to follow-up.

Treatment (or intervention)

As this study is designed to establish the prevalence of hypopituitarism in patients with mTBI, no treatment or intervention will be included. The primary endpoint of this study will be a confirmed deficit in one or multiple hormones.

Study variables and measures

Eligible veteran patients who have been diagnosed with PTSD or depression and are either currently receiving any form of psychiatric treatment will be screened or rescreened with the TRCS and CBTIE protocol. Those that are found to have a positive history of mTBI and those that are deemed to have treatment resistant depression will be eligible for the study and consented for further study involvement.

The primary variable being assessed will be levels of neurohormones in participants compared to the currently accepted normal reference ranges. Specifically, the levels of IGF-1, LH, FSH, free testosterone, cortisol, TSH, T3/T4, and DHEA, collected via venous blood draws. Secondary variables will include age, branch of military service, time since last known mTBI, and both number and severity of potential mTBI symptoms.

Recruitment

Subjects for this study will be veteran patients recruited from VA hospitals or VA Mission Act-approved clinics. The electronic medical record system used by the VHA allows healthcare providers to access the entirety of their patient's medical record. This will allow a primary care provider (PCP) to identify eligible participants by their recorded diagnoses. Since the VHA also uses a secure intranet to allow communication by e-mail, primary care providers (PCP) can be sent information regarding the proposed study directly. These providers will then receive information regarding the study, what information is needed to give to their patients, and the proper consent documents. Patients within the VA healthcare system that have already received diagnoses of PTSD or depression and met the above inclusion criteria will be interviewed by their PCP and screened for mTBI using the established TRCS and CBTIE protocol. Patients that screen positive for mTBI, regardless of when the trauma occurred, will then be informed of the study and offered participation. Patients that meet the inclusion criteria and agree to participate in the study will then be consented by their primary care provider. Providers that have individuals eligible for the study that are consented will send the results of each sample collection to the primary investigator.

Data collection

Plasma and serum samples of study participants will be taken as soon as possible. The initial sample will serve as the patient's baseline pituitary hormone levels for comparison of future samples. Most, if not all, VA hospitals are equipped to both obtain

the serum samples via phlebotomy and test the samples using in-house laboratories. Since the VA employs laboratory personnel, no additional staffing will be necessary. The results are reported via the VA's electronic medical record (EMR) system, which can be accessed directly by the participates healthcare provider.

After the baseline sample is obtained, further hormonal assessments can be obtained on a six-month basis, until a deficit is identified, the patient withdraws from the study, or a breakthrough in the patients' psychiatric treatment occurs and their symptoms resolve.

To ensure uniformity of sample draws and reported results, the study will use the preferred serum assays currently used in practice at VA hospitals and the reference range for abnormal values will be dependent the currently acceptable values as described by the VA laboratories. In the event that different assays or data ranges are used, each sample will have the date, location of sample draw, and manufacturer of assay recorded and reported in the results of the study.

Data analysis

The results of each participants hormone panel will be collected and analyzed by a primary investigator, who will receive the results directly from the subjects' PCP. This primary investigator will compile the data and assess for deficiencies of pituitary hormones by comparing the serum assay levels taken from participants to known hormone reference ranges (previously shown in figure 1). Results will then be reported as being normal (within normal limits) or deficient (below reference range). Once the study is completed, subject data can be further stratified by age, comorbid conditions, and

severity of psychiatric conditions. The results can be reported as an overall pooled prevalence (total number of participants with a confirmed pituitary hormone deficiency), as well as a prevalence of individual hormone deficiency.

The data from participants that meet inclusion criteria but are lost to follow-up, either by requesting to no longer participate in the study, no longer engage in healthcare by their PCP, or by death, will not be reported in the results of study.

Timeline and resources

Fall – Winter 2020	Submit for IRB approval
January 2021 – March 2021	Patient recruitment
April 2021 – December 2021	Data collection Data reporting and analysis
January 2022	Completion of data analysis Study results submitted for peer review

Approval from the Boston University Medical Campus Institutional Review Board (BUMC-IRB) is expected to take at least 3 months. Patient recruitment may take as long as one year in order to reach a goal sample size of 800 subjects, though data collection may begin as soon as a subject is consented. Since the VA employs all of the necessary personnel and are equipped with the necessary hormone assays, laboratories, and EMR, no further acquisition will be needed.

Institutional Review Board

This study will involve human subjects and thus will require approval by Institutional Review Board (IRB) board review and approval before it is performed. The This study qualifies for expedited review as defined by section 10.2.2.4.1.2 of the Human Research Protection Program (HRPP), category 2. This expedited review category falls under the Common Rule and applies due to the proposed study's requirement to collect blood samples by venipuncture from adults, with the amount drawn not to exceed 550 milliliters in one 8-week period.

CONCLUSION

Discussion

The goal of this study is to establish the prevalence of TBI-induced hypopituitarism among veteran patients being treated for PTSD and/or depression, which is currently largely unknown. Despite increasing attention and research being given to mTBI, there is much still to be learned about the pathophysiology of its long-term sequelae. Given the relatively high incidence of mTBI, PTSD, and depression within the VA and military, this population serves as a good starting point for establishing how common post-TBI pituitary dysfunction may be.

If the percentage of those within the VA healthcare system is seen to be substantial, clinicians can use this information to create a clinical decision guideline to make recognition of this disease process easier and more efficient. Given the high incidence of mTBI across the US and world, this study will have good generalizability for application to other subgroups, such as contact sport athletes, as well as to the population at large. Further studies focused on the neuroinflammation and its long-term effects following mTBI has the potential to identify biomarkers that may be used to identify those at risk of developing psychiatric and cognitive manifestations of pituitary dysfunction.

One inherent obstacle to this study will be recruiting enough participants with a reported history of mTBI. As discussed previously, diagnosis of mTBI by VA standards is based on symptoms experienced acutely after the injury and typically involves either brief loss of consciousness or some degree of post-injury amnesia. As we have seen in

other studies, the neuroinflammation suspected to cause pituitary dysfunction can still occur in the absence of these symptoms. So, when prompted with screening questions regarding either loss of consciousness or inability to remember post-injury events, a patient may report not experiencing either, resulting in a negative mTBI screen and potentially introducing a sample bias. Another limitation involved with asking patients specific questions regarding loss of consciousness or memory impairment is the risk of recall bias. If a patient suffered from memory loss following a head strike, they may not remember just how significant the injury was. Memory loss due to the injury itself, as well as psychologic trauma due to the event that caused the head injury represents potential for recall bias, as well as confounding the study results, as the individual may not remember if and for long they lost consciousness.

Given these limitations, further studies will likely need to be performed to increase the strength of proposed study's findings. Such studies might include stratifying participants by age, time-lapse from injury to onset of symptoms, degree/severity of symptoms, and intervention vs non-intervention sub-groups. At this current time, without knowing the prevalence or significance of this problem, the strength of these studies would be low.

Summary

Traumatic brain injuries effect a large number of individuals in both the military and the civilian population and can lead to a host of neurologic and psychiatric symptoms. Though mTBI is often viewed as a transient event with no long reaching

effects, there are some that suffer from a wide range of symptoms for months to years following the trauma. While research of neuroinflammation following mTBI has been increasing in recent years, there is still much that is unknown regarding the long-term implications and whether or not this can cause pituitary dysfunction.

By establishing a better understanding of the prevalence of this mTBI-induced dysfunction, this study can help researchers and clinicians design better ways to evaluate, monitor, and treat patients presenting with neuropsychiatric manifestations. Even with the vast suspected underreporting of mTBI, these injuries account for the majority of TBI related hospital visits. It can be further suspected that individuals with history of mTBI, however remote, that are suffering from treatment resistant PTSD, depression, anxiety, cognitive impairment, or any combination of neuropsychiatric symptoms may have underlying hormonal dysfunction.

Clinical and/or public health significance

In the absence of obvious trauma and/or abnormalities on head imaging, TBI-induced neuropsychiatric presentations are improperly managed with medications. Not only are these patients potentially being medically mismanaged, they are being told that their problems can only be treated with therapy or as their symptoms arise. The medical approach typically involves polypharmacy that brings with it a host of unwanted and potentially dangerous side effects. As the treatment fails or as the list of medications these people are prescribed grows, frustration and mistrust may begin to manifest with their healthcare providers. These patients in particular are at risk of hazardous self-

medication and even self-harm. The disastrous effects of this technique are well known in the veteran population and seen far too commonly in individuals suffering from psychiatric disorders such as PTSD, depression, anxiety, and so on.

Proper identification and treatment of the psychologic conditions stemming from hormonal dysfunction has shown to be successful in increasing the overall well-being of the veterans suffering from them. The cost of this treatment is also much lower than the amount that is being spent by the VHA in their treatment of PTSD and TBI.

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