

Breakthrough **Neurosteroidal** Treatment For Traumatic Brain Injury

By Michael Downey

In February, the US Office of Naval Research announced its support of research at the University of Texas at Arlington that appears to explain how shock waves cause **traumatic brain injury** (TBI). Waves of energy cause tiny bubbles, or “microcavitations,” to form, pop, and disappear so quickly that they can’t be detected by brain-imaging—but can seriously unbalance an array of biochemical compounds.¹

Invisible or not, these biochemical disruptions have long been successfully treated by interventional endocrinologist Dr. Mark Gordon. His insightful approach recognized that it is disrupted neurosteroidal function—not simply physical brain damage—that creates the sustained TBI neurological deficits.

By restoring neurosteroids to pre-injury levels, Gordon is successfully treating the depression, angry outbursts, anxiety, and mood swings commonly suffered by patients with TBI, a condition afflicting over two million Americans annually.

The government is slow to accept the link between TBI and neurosteroid deficiencies, resulting in many veterans being misdiagnosed and instead, treated for post-traumatic stress disorder. Fortunately, thanks to this innovative therapy, a growing number of affected veterans and others are getting their lives back on track. > > >

Tiny ‘Bubbles’ May Explain Why TBI Often Goes Untreated

Soldiers are outfitted with body armor that can withstand shrapnel from a bomb or other explosive device. But no amount of armor can protect them from an explosion’s invisible but devastating threat—the shock wave. (blast wave)

“Shock waves travel faster than sound,” says Dr. Timothy Bentley, a program manager in the Warfighter Performance Department at the Office of Naval Research (ONR). “This energy wave can cause subtle yet damaging effects on the brain.”¹

For this reason, the ONR is supporting research at the University of Texas at Arlington focused on the idea that explosive shock waves cause energy-packed bubbles—under a millimeter

across—to form and pop so quickly that they can damage surrounding cells and tissue while remaining undetectable via MRI or other brain scan.¹ (millimeter = 1/25 of an inch)

The collapse of these momentary “microcavitations” can compromise, and cause leakage through, the blood-brain barrier—a network of tightly packed blood vessels in the brain that allows healthy molecules to enter the brain from the bloodstream and prevents the entry of harmful ones.¹

This research into how shock waves can affect delicate brain tissue may explain why so many TBI injuries—involving neurosteroid imbalances that trigger memory loss, headaches, and a host of cognitive, psychological, and emotional symptoms—often go untreated.

Neurosteroids are a group of steroidal hormones synthesized by the brain. They regulate neuron growth, myelination, and the formation of synapses between neurons in the nervous system (synaptogenesis).

When people use the term “hormones,” they are usually referring to those that are produced in the peripheral glands throughout the body—but more correctly, these hormones are more called *neuroactive steroids*.

But *neurosteroid* dysfunction can result in depression, anxiety, panic attacks, phobias, psychoses, and frequently suicide. Neurosteroids also play a crucial role in regulating neuroactive steroids in glands throughout the body.

It may seem odd that shock waves—without causing physical brain damage—can still disrupt neurosteroid production and, consequently, body-wide hormonal balance. The answer lies in the secondary injury processes that occur after the initial injury. Let’s examine these secondary consequences.

The Critical *Secondary* Effects Of Traumatic Brain Injuries

Individuals affected by traumatic brain injury can suffer a broad spectrum of effects that often show up only decades later² and continue to progressively worsen. Conventional medical treatment seldom achieves substantial recovery, and persistent symptoms can become extremely disabling.³

There can be both a primary and secondary injury with TBI.⁴ Primary injury⁵ occurs from the forces at the time of injury and is believed to be irreversible.⁶ However, the complex secondary mechanisms play a crucial role in the delayed progression of brain damage—presenting novel opportunities for therapeutic strategies. One of these secondary injury processes that may promote latent neuronal death is post-traumatic inflammation, which increases blood-brain barrier permeability, cerebral edema, and intracranial pressure, resulting in neuronal dysfunction following TBI.⁷

Some of the 330,000 soldiers afflicted in the past 15 years with one or more TBIs from blast shock waves have recovered quickly, but studies suggest that many go on to suffer lingering cognitive problems.⁸

While veterans are commonly affected, TBI can affect anyone—car accident victims, construction workers, fall-prone individuals, and contact sport athletes. In fact, TBI is a leading cause of death and disability, the greatest cause of coma, the leading player in trauma-caused disability, and the top cause of brain damage in children and young adults.⁹⁻¹¹

Next, we'll learn about the devastating neurosteroid deficiencies that can plague TBI victims.

Multiple Imbalances

Many studies demonstrate that hypopituitarism—where the pituitary fails to produce normal hormone levels—is relatively common following TBI.¹²⁻¹⁵ Sometimes, however, hypopituitarism diagnoses are not made for over 20 years after the injury.¹⁶

TBI patients who have a deficiency in growth hormone—the most common insufficiency in TBI—exhibit greater deficits in attention, executive functioning, memory, and emotion than patients with normal levels.¹⁷ Growth hormone binds to brain receptors that are especially dense in regions responsible for learning and memory^{18,19}—perhaps explaining why declining levels are associated with poorer cognitive function.

Growth hormone increases survival of damaged nerve cells and promotes regeneration of nerve tissue.²⁰⁻²² It also increases body-wide receptors for other hormones, helping to overcome the effects of their deficiencies.²³⁻²⁶

Growth hormone levels fall with age and are especially low in Alzheimer's disease.²⁷⁻³¹ TBI patients' symptoms often mirror the cognitive decline and memory loss seen with aging and Alzheimer's disease.

The sex hormones are also closely related to cognitive function and dysfunction. They can function directly as neurotransmitters in the central nervous system.³² At least 16% of long-term TBI survivors develop hypogonadism, meaning that the testes in men or the ovaries in women produce insufficient levels of sex hormones. However, it is estimated that these deficiencies are not identified or treated in most individuals.¹²

Some might assume that sex hormone insufficiency simply relates to sexual desire. But whether due to TBI or aging, low sex hormone levels are increasingly linked to dementia. For instance, age-related declines in sex hormones significantly contribute to Alzheimer's disease risk in both men and women.³³ In a study involving over 500 aging men and women, optimum testosterone levels were linked with better performance on the Mini-Mental Status Examination.³⁴ Several other studies concluded that testosterone levels are positively associated with multiple aspects of cognitive function.^{35,36}

Scientists have found that recovery of patients with TBI is greater in those with higher testosterone levels.³⁷ But despite the demonstrated links between sex hormones and neuroprotection, virtually no physicians use sex hormones to treat TBI.

“For traumatic brain injury patients,” says Dr. Mark L. Gordon, traumatic brain injury treatment specialist at Millennium Health Centers in Los Angeles, “any proper diagnosis and treatment protocol should begin with baseline testing of testosterone, growth hormone, thyroid, cortisol, insulin and Vitamin D.”

Although there is copious evidence that patients with traumatic brain injury suffer from hypothalamic-pituitary hormonal imbalances—and ample expert recommendations for rigorous hormone testing—few physicians bother to test neurosteroid levels in brain-injured patients.^{17,18,38} And worse, despite compelling studies showing the benefits of neurosteroid replacement, virtually no US physician offers such therapy.

Fortunately, thanks to Gordon’s groundbreaking work, along with a handful of forward-thinking physicians, there is promise for the almost two million Americans afflicted with this condition.³⁹

New Hope For TBI Patients At Millennium Health Centers

Using cutting-edge, neurosteroid replacement techniques, Gordon and his colleagues are helping to change the way we think about traumatic brain injuries, their symptoms, and how to treat them effectively. In his clinical practice, he continues to develop new protocols that may revolutionize the devastating impact of TBIs.

“Whether caused by direct impact or by acceleration alone, the secondary injuries that can result from brain trauma occur in the minutes and days following injury,” says Gordon. “And these can include alterations in cerebral blood flow and increased pressure within the skull—contributing substantially to damage from the initial injury.”

An array of resulting symptoms—physical, cognitive, emotional, and behavioral effects—can appear immediately or in the weeks or years following the injury. These symptoms often go unrecognized or unnoticed, especially in mild traumatic brain injury cases.

“Insidious traumatic brain injury can be difficult to detect,” Gordon says. “Localized damage to the frontal and occipital lobes occurs when the brain collides with the skull. Increasingly, we are discovering that traumatic brain injury is also a causative factor for accelerated neurosteroid deficiencies.”

The ways that neurosteroid deficiencies can manifest are numerous, says Gordon, including:

- depression
- outbursts of anger
- anxiety
- mood swings
- memory loss

- inability to concentrate
- learning disabilities
- sleep deprivation
- increased risk for heart attacks
- strokes
- high blood pressure
- diabetes
- loss of libido
- menstrual irregularities
- premature menopause
- obesity
- loss of lean body mass
- muscular weakness, and
- a number of other medically documented conditions.

Especially tragic among veterans, says Gordon, is the fact that psychological damage due to traumatic brain injury is often erroneously diagnosed as post-traumatic stress disorder, commonly known as PTSD.

The neurosteroid-balancing therapy that Gordon provides is changing lives, especially among military veterans. And this remarkable breakthrough originated when, acting on a hunch, he investigated a wealth of published literature to help understand what was occurring in patients whose symptoms had long outlasted the immediate effects of their acute injuries.

The TBI Link To Pituitary Dysfunction

Dr. Gordon's research strongly suggested that TBI often causes pituitary dysfunction, confirming his initial hunch.⁴⁰

He found that between 50% and 76% of traumatic brain injury victims show some loss of pituitary neurosteroid function immediately following brain injury.^{41,14,15} Generally, the more severe the original brain injury, the more profound the deficits. However, neurosteroid deficiency or insufficiency—in the low-normal range—is seen even in patients with *mild* traumatic brain injury.⁴²⁻⁴⁶

Although about 58% of TBI patients recover normal pituitary function within a year of injury, a shocking 52% develop new pituitary neurosteroid deficiencies after one year.^{47,48} These deficits include reductions in many pituitary hormones, including those that regulate the thyroid gland, the adrenal glands (which produce cortisol, DHEA, and other vital hormones), the gonads (where estrogen and testosterone are produced), and growth hormone.^{12,14,15,49}

The severity of the neurosteroid deficiencies correlated strongly with the kinds of symptoms that Gordon was seeing. For instance, patients with growth hormone deficiency or insufficiency had significantly worse disability scores, greater depression rates, poorer life quality, lower energy,

greater fatigue, and worse emotional well-being, compared to brain injury patients with normal neurosteroid levels.^{50,51}

Gordon's research clearly confirmed that TBI victims did, in fact, often have pituitary neurosteroid deficiencies or insufficiencies, especially in growth hormone. And they are closely associated with the persistent neurological, psychological, and emotional deficits so tragically common in brain injury survivors.

Hypothalamus Dysfunction

Many people are aware that powerful biological regulatory molecules—commonly known as “hormones,” but more precisely called neuroactive steroids—are the products of endocrine glands located throughout the body, but critically, that's not the whole story. Virtually all endocrine glands are controlled by the pituitary gland, located inside the skull at the base of the brain. Because of its powerful influence on the other endocrine glands, the pituitary is seen as the “master gland.” Yet even this master gland is subject to a higher level of control.

An ancient brain structure called the hypothalamus has a direct connection to the pituitary through a unique network of veins. Regulatory molecules from the hypothalamus tell the pituitary how much of its own neurosteroids and hormone-releasing factors to produce. And the hypothalamus, as part of the brain itself, receives constant neurological inputs from all over the body, creating numerous feedback loops. It is those feedback loops that maintain a steady balance between extreme biochemical states.

This connection between the brain's hypothalamus and the endocrine system's pituitary is called *neuroendocrine* function. Although it may seem obvious, medical science is only beginning to recognize that trauma to the brain, even seemingly minor trauma, can damage the hypothalamic-pituitary system and profoundly affect neurosteroidal function.

In fact, most people—including most physicians—assume that the neurological deficits that follow brain injury simply result from disruption to brain tissue. In this simplistic model, a blow to the head causes the brain to be “rattled,” triggering bleeding, bruising, and other large-scale injuries that can be seen on MRI and CT scans. Some of the deficits that a brain-injured person will sustain can be predicted by the location and severity of the visible damage on those scans, but TBI victims frequently sustain neurological deficits that exceed what brain scans would normally indicate. People with so-called “minor” traumatic brain injury—the largest group of brain-injured patients—have no visible damage at all on brain scans.

Medical orthodoxy is slow to change. But Gordon's fresh approach and insight has already brought new recognition that it's not simply physical brain damage, but rather disrupted neurosteroidal function, that creates the sustained neurological deficits suffered by TBI victims.

Changing TBI Victims' Lives

Gordon's clinic provides comprehensive testing to assess how well the hypothalamic-pituitary system is functioning, and secondary testing to determine how the target endocrine glands are

affected. Those findings are correlated with a complete history and detailed physical examination to create an individualized treatment protocol.

Physiologic doses, not megadoses, are used for each neurosteroid to slowly restore levels to the middle of the optimum range, monitoring cognitive and physical functions monthly.

Gordon's patient success stories confirm that restoring neurosteroid levels to their optimal and pre-injury levels produces remarkable recovery of many impaired functions. His work is attracting international attention, and he is actively recruiting physicians to learn his protocols.

Patients typically respond within weeks to the Millennium protocol. And the responses are dramatic.

Veterans constitute a large TBI population. But because the government is slow to accept the link between TBI and neurosteroid deficiencies, many are misdiagnosed and instead, treated for PTSD.

“Part of the reason is that the military and doctors see testosterone as a *bodybuilder drug*,” explains Gordon, “rather than a natural substance produced in our bodies.”

“Science now has the ability to map the entire brain, and we now know exactly where growth hormone works on mood, what pathways it uses,” he says. “The military is simply not prepared to go to the depths that we have in the private sector.”

Andrew Marr is one of many veterans who can attest to that. The former Army Special Forces Green Beret—and patient of Gordon—suffered multiple TBIs. Marr is now heading a campaign to raise funds to help other veterans benefit from this therapy. He says that it has changed his life, while his numerous and powerful, previously prescribed medications only made things worse.

“It's highly individualized. No two people are the same,” Marr explains. “Whatever you're found to be deficient or insufficient in, that's exactly what is going to be replaced.”

Summary

Shock waves may cause momentary “bubbles” in the brain that leave millions of traumatic brain injury (TBI) victims with substantially impaired physical, emotional, and cognitive health.

Mainstream medicine offers little to overcome these long-term pathologies and military veterans' TBIs are often misdiagnosed as depression or PTSD.

Dr. Mark Gordon's discovery that TBI damages the hypothalamus and triggers pituitary gland dysfunction prompted him to identify and treat the resulting neurosteroid deficiencies in his TBI patients.

A growing number of veterans and others attest to the failure of mainstream TBI treatment and the remarkable success of Gordon's innovative, highly individualized therapy.

Patients with traumatic brain injury, or their family members, may visit Millennium's website at www.TBImedlegal.co where a new patient intake form can be filled out to start the process of evaluation. Information at the website also lets patients know what a typical course of treatment involves.

If you have any questions on the scientific content of this article, please call a Life Extension[®] Health Advisor at 1-866-864-3027.

BEGIN SIDEBAR 1

What You Need To Know

- Shock waves leave millions of traumatic brain injury (TBI) victims physically, emotionally, and cognitively impaired.
- Mainstream medicine offers little to treat these long-term pathologies, frequently misdiagnosing TBI as depression or PTSD.
- Dr. Mark Gordon discovered that TBI damages the hypothalamus and triggers pituitary dysfunction and now successfully treats the resulting neurosteroid deficiencies in his TBI patients.
- Many veterans and others—disappointed with the failure of mainstream TBI treatment—are experiencing remarkable success with Gordon's innovative, highly individualized therapy.

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How A Dedicated Green Beret With TBI Is Helping Other Veterans

The Warrior Angels Foundation (WAF) is a nonprofit charitable organization, cofounded and managed by Andrew Marr, former Army Special Forces Green Beret—and TBI patient of Dr. Mark Gordon.

Marr is spearheading a campaign to raise donations to allow other TBI-affected vets to benefit from this remarkable therapy. He says that it has changed his life, while his previously prescribed medications only made things worse.

Veterans returning from battle constitute a large TBI patient population. Nearly 314,000 cases of traumatic brain injury have been diagnosed since 2000, with the Army's total far outpacing other branches of the military. But many are misdiagnosed and instead, treated for depression or

PTSD. Those with so-called “minor traumatic brain injury,” who comprise the largest group of brain-injured patients, have no visible damage at all on brain scans.

The government is slow to accept the link between TBI and neurosteroid deficiencies and will not pay for Gordon’s Millennium Clinic treatment protocol. This is in spite of the fact, Marr says, that it is vastly less costly than the multiple prescriptions and other therapies that the Veterans’ Administration (VA) currently provides.

“When you have 360,000-plus GIs coming back from war with traumatic brain injury, it gets expensive,” Gordon says, “especially when you have to start addressing neurosteroid deficiencies.”

In 2006, the army’s surgeon-general established the Traumatic Brain Injury Task Force to establish a clear picture of the processes and research involved with helping TBI-affected service members transition to civilian life. The task force was designed to assess how the army addressed aspects of TBI care and made recommendations for improvement. However, Gordon believes the bottom line is that a task force can do little if the military doesn’t want to pay for treatment.

Conventional medical dosage for testosterone is 200 to 300 milligrams per week, which Gordon has shown is far too high.

“For example, a typical 25- to 35-year-old male naturally generates 4 to 10 milligrams daily or 60 milligrams per week,” he explains. “Using supraphysiological dosages of testosterone—as military doctors are doing—can have significant side-effects if not monitored closely. We can achieve similar benefits at one-quarter the dose without the risk factors.”

While Gordon admits that interventional endocrinology may not be for everyone, patients such as soldiers will eagerly seek it out when traditional doctors have hit a wall and are unable to fix ongoing issues. Military veterans have described to him the sheer difficulty of getting anything done through the military.

“Part of the reason is that the military and doctors see testosterone as a *bodybuilder drug*, rather than a natural substance produced in our bodies,” explains Gordon. “It makes no sense that they can readily accept insulin use for diabetes, but not testosterone. They’re both natural hormones, flowing naturally through our bodies.”

Many of the WAF-assisted patients who have received Gordon’s individualized neurosteroid-balancing protocol experienced a significant turnaround within weeks of beginning treatment.

“We’re taking out the middleman of the waiting room and [Veteran’s Affairs] and reducing the costs of what the VA and government spends on TBI patients,” says Marr. He notes that, as an individual’s therapy continues—and fewer tests and treatments are required—expenses go down.

In its first year, the Warrior Angels Foundation raised over \$100,000 to aid in the treatment of more than 100 service members and veterans—but the organization has a waiting list of over 700 veterans. The VA does not offer Dr. Gordon’s neurosteroid-balancing treatment, nor will they pay for it.

Those wishing to learn more or to help with fundraising can visit <http://www.waftbi.org/>.

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Millennium Clinic's Traumatic Brain Injury Neurosteroid Test Panel

- IGF-1
- Free testosterone
- Estrogens (female only)
- Cortisol
- TSH
- T3/T4
- DHEA

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References:

1. Available at: <http://www.onr.navy.mil/en/Media-Center/Press-Releases/2016/Explosive-Shock-Waves-Brain-Injury.aspx>.
2. Gavett BE, Stern RA, McKee AC. Chronic traumatic encephalopathy: a potential late effect of sport-related concussive and subconcussive head trauma. *Clin Sports Med* . 2011 Jan;30(1):179-88.
3. High WM, Jr, Briones-Galang M, Clark JA, et al. Effect of growth hormone replacement therapy on cognition after traumatic brain injury. *J Neurotrauma*. 2010 Sep;27(9):1565-75.
4. Kumar A, Loane DJ. Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. *Brain Behav Immun*. 2012 Nov;26(8):1191-201.
5. Margulies S, Hicks R; Combination Therapies for Traumatic Brain Injury Workshop Leaders, Combination therapies for traumatic brain injury: prospective considerations. *J Neurotrauma*. 2009 Jun;26(6):925-39.
6. Wei J, Xiao GM. The neuroprotective effects of progesterone on traumatic brain injury: current status and future prospects. *Acta Pharmacol Sin*. 2013 Dec;34(12):1485-90.
7. Si D, Li J, Liu J, et al. Progesterone protects blood-brain barrier function and improves neurological outcome following traumatic brain injury in rats. *Exp Ther Med*. 2014 Sep;8(3):1010-14.
8. Available at: <http://www.foxnews.com/health/2015/09/11/former-army-sergeant-raising-funds-for-hormone-replacement-therapy-to-treat.html?intcmp=hphz02>.
9. Alves OL, Bullock R. "Excitotoxic damage in traumatic brain injury." In Clark RSB, Kochanek P. Brain injury. Boston: Kluwer Academic Publishers. 2001. p. 1.
10. Zink BJ. Traumatic brain injury outcome: concepts for emergency care. *Ann Emerg Med*. 2001 Mar;37(3):318-32.
11. Hannay HJ, Howieson DB, Loring DW, Fischer JS, Lezak MD. "Neuropathology for neuropsychologists." In Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. Oxford [Oxfordshire]: Oxford University Press. 2004. pp. 158-62.

12. Hohl A, Mazzuco TL, Coral MH, Schwarzbald M, Walz R. Hypogonadism after traumatic brain injury. *Arq Bras Endocrinol Metabol.* 2009 Nov;53(8):908-14.
13. Klose M, Juul A, Struck J, Morgenthaler NG, Kosteljanetz M, Feldt-Rasmussen U. Acute and long-term pituitary insufficiency in traumatic brain injury: a prospective single-centre study. *Clin Endocrinol (Oxf).* 2007 Oct;67(4):598-606.
14. Agha A, Rogers B, Mylotte D, et al. Neuroendocrine dysfunction in the acute phase of traumatic brain injury. *Clin Endocrinol (Oxf).* 2004 May;60(5):584-91.
15. Agha A, Rogers B, Sherlock M, et al. Anterior pituitary dysfunction in survivors of traumatic brain injury. *J Clin Endocrinol Metab.* 2004 Oct;89(10):4929-36.
16. Aimaretti G, Ghigo E. Traumatic brain injury and hypopituitarism. *ScientificWorldJournal.* 2005 Sep 15;5:777-81.
17. Leon-Carrion J, Leal-Cerro A, Cabezas FM, et al. Cognitive deterioration due to GH deficiency in patients with traumatic brain injury: a preliminary report. *Brain Inj.* 2007 Jul;21(8):871-5.
18. van Dam PS, Aleman A, de Vries WR, et al. Growth hormone, insulin-like growth factor I and cognitive function in adults. *Growth Horm IGF Res.* 2000 Apr;10 Suppl B:S69-73.
19. Creighton WM, van Dam PS, Koppeschaar HP. The role of the somatotrophic system in cognition and other cerebral functions. *Semin Vasc Med.* 2004 May;4(2):167-72.
20. Muresanu DF, Sharma A, Sharma HS. Diabetes aggravates heat stress-induced blood-brain barrier breakdown, reduction in cerebral blood flow, edema formation, and brain pathology: possible neuroprotection with growth hormone. *Ann N Y Acad Sci.* 2010 Jun;1199:15-26.
21. Pathipati P, Gorba T, Scheepens A, Goffin V, Sun Y, Fraser M. Growth hormone and prolactin regulate human neural stem cell regenerative activity. *Neuroscience.* 2011 Sep 8;190:409-27.
22. Sanders EJ, Lin WY, Parker E, Harvey S. Growth hormone promotes the survival of retinal cells in vivo. *Gen Comp Endocrinol.* 2011 May 15;172(1):140-50.
23. Herndon DN, Hawkins HK, Nguyen TT, Pierre E, Cox R, Barrow RE. Characterization of growth hormone enhanced donor site healing in patients with large cutaneous burns. *Ann Surg.* 1995 Jun;221(6):649-56; discussion 56-9.
24. Ono M, Miki N, Murata Y, Demura H. Hypothalamic growth hormone-releasing factor (GRF) regulates its own receptor gene expression in vivo in the rat pituitary. *Endocr J.* 1998 Apr;45 Suppl:S85-8.
25. Qin Y, Tian YP. Hepatic adiponectin receptor R2 expression is up-regulated in normal adult male mice by chronic exogenous growth hormone levels. *Mol Med Report.* 2010 May-Jun;3(3):525-30.
26. Wyse B, Sernia C. Growth hormone regulates AT-1a angiotensin receptors in astrocytes. *Endocrinology.* 1997 Oct;138(10):4176-80.
27. Aleman A, de Vries WR, de Haan EH, Verhaar HJ, Samson MM, Koppeschaar HP. Age-sensitive cognitive function, growth hormone and insulin-like growth factor 1 plasma levels in healthy older men. *Neuropsychobiology.* 2000 Jan;41(2):73-8.
28. Gasperi M, Castellano AE. Growth hormone/insulin-like growth factor I axis in neurodegenerative diseases. *J Endocrinol Invest.* 2010 Sep;33(8):587-91.
29. Malek M, Zahedi Asl S, Sarkaki A, Farbood Y, Doulah AH. The effect of intra-hippocampal injection of growth hormone on spatial learning and memory in animal model of Alzheimer's disease. *Pak J Biol Sci.* 2009 Sep 15;12(18):1237-45.

30. Lijffijt M, Van Dam PS, Kenemans JL, et al. Somatotrophic-axis deficiency affects brain substrates of selective attention in childhood-onset growth hormone deficient patients. *Neurosci Lett*. 2003 Dec 19;353(2):123-6.
31. Quik EH, Conemans EB, Valk GD, Kenemans JL, Koppeschaar HP, Dam PS. Cognitive performance in older males is associated with growth hormone secretion. *Neurobiol Aging*. 2012 Mar;33(3):582-7.
32. Balthazart J, Ball GF. Is brain estradiol a hormone or a neurotransmitter? *Trends Neurosci*. 2006 May;29(5):241-9.
33. Vest RS, Pike CJ. Gender, sex steroid hormones, and Alzheimer's disease. *Horm Behav*. 2013 Feb;63(2):301-7.
34. Hogervorst E, Matthews FE, Brayne C. Are optimal levels of testosterone associated with better cognitive function in healthy older women and men? *Biochim Biophys Acta*. 2010 Oct;1800(10):1145-52.
35. Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab*. 2002 Nov;87(11):5001-7.
36. Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. *J Clin Endocrinol Metab*. 1999 Oct;84(10):3681-5.
37. Young TP, Hoaglin HM, Burke DT. The role of serum testosterone and TBI in the in-patient rehabilitation setting. *Brain Inj*. 2007 Jun;21(6):645-9.
38. Aimaretti G, Ghigo E. Traumatic brain injury and hypopituitarism. *ScientificWorldJournal*. 2005 Sep 15;5:777-81.
39. Available at: http://www.legion.org/documents/legion/pdf/TBI.PTSD_hinds.pdf.
40. Leal-Cerro A, Flores JM, Rincon M, et al. Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. *Clin Endocrinol (Oxf)*. 2005 May;62(5):525-32.
41. Klohe M, Juul A, Struck J, Morgenthaler NG, Kosteljanetz M, Feldt-Rasmussen U. Acute and long-term pituitary insufficiency in traumatic brain injury: a prospective single-centre study. *Clin Endocrinol (Oxf)*. 2007 Oct;67(4):598-606.
42. Krahulik D, Zapletalova J, Frysak Z, Vaverka M. Dysfunction of hypothalamic-hypophysial axis after traumatic brain injury in adults. *J Neurosurg*. 2010 Sep;113(3):581-4.
43. Urban RJ, Harris P, Masel B. Anterior hypopituitarism following traumatic brain injury. *Brain Inj*. 2005 May;19(5):349-58.
44. Bigler ED. Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *J Int Neuropsychol Soc*. 2008 Jan;14(1):1-22.
45. Ives JC, Alderman M, Stred SE. Hypopituitarism after multiple concussions: a retrospective case study in an adolescent male. *J Athl Train*. 2007 Jul-Sep;42(3):431-9.
46. Tanriverdi F, Unluhizarci K, Kelestimur F. Pituitary function in subjects with mild traumatic brain injury: a review of literature and proposal of a screening strategy. *Pituitary*. 2010 Jun;13(2): 146-53.
47. Tanriverdi F, Senyurek H, Unluhizarci K, Selcuklu A, Casanueva FF, Kelestimur F. High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. *J Clin Endocrinol Metab*. 2006 Jun;91(6):2105-11.

48. Agha A, Phillips J, O'Kelly P, Tormey W, Thompson CJ. The natural history of post-traumatic hypopituitarism: implications for assessment and treatment. *Am J Med.* 2005 Dec;118(12):1416.
49. Hohl A, Daltrozo JB, Pereira CG, et al. Late evaluation of the pituitary-gonadal axis in survivors of severe traumatic brain injury. *Arq Bras Endocrinol Metabol.* 2009 Nov;53(8):1012-9.
50. Bavisetty S, McArthur DL, Dusick JR, et al. Chronic hypopituitarism after traumatic brain injury: risk assessment and relationship to outcome. *Neurosurgery.* 2008 May;62(5):1080-93; discussion 93-4.
51. Kelly DF, McArthur DL, Levin H, et al. Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury. *J Neurotrauma.* 2006 Jun;23(6):928-42.