ABSTRACT

Traumatic brain injury (TBI), typically resulting from vehicle accidents or acts of violence, is a major public health concern. Survivors often face lifelong impairments affecting functional status, memory, cognition, language, and mood, as well as physical functioning and metabolism. Within the past three years, a clear cause and effect has been established – post TBI hormonal deficiency syndrome. Prior to this new knowledge patients have been treated with symptomatic protocols that simply did not work. There is an increasing amount of evidence to suggest that post TBI hormonal deficiency syndrome affects many people who have sustained TBI and mild TBI, and research is now beginning to show that replacement of deficient hormones can lead to significant improvements. This paper will consider the incidence, clinical course, diagnosis, and treatment of post TBI hormonal deficiency syndrome.

INTRODUCTION

Traumatic brain injury (TBI), typically resulting from vehicle accidents or acts of violence, is a major public health concern. Survivors often face lifelong impairments affecting functional status, memory, cognition, language, and mood, as well as physical functioning and metabolism. Within the past three years, a clear cause and effect has been established – post TBI hormonal deficiency syndrome. Prior to this new knowledge patients have been treated with symptomatic protocols that simply did not work. There is an increasing amount of evidence to suggest that post TBI hormonal deficiency syndrome affects many people who have sustained TBI and mild TBI, and research is now beginning to show that replacement of deficient hormones can lead to significant improvements.

POST TRAUMATIC BRAIN INJURY HORMONAL DEFICIENCY SYNDROME

Incidence

An estimated 1.9 million Americans sustain a TBI each year. Approximately half of these cases result in at least short-term disability, and approximately 52,000 of those people die from their injuries. Of those that survive, many will develop progressive hormonal deficiencies, which lead to post concussion syndrome or post TBI hormonal deficiency syndrome, a cascade of deficiencies of hormones that will affect every aspect of functioning and will have a dramatic effect upon the patient's quality of life. Merriam et al found that just 20% of adults with growth hormone (GH) deficiency have a history of childhood-onset GH deficiency. Therefore, the remaining 80% are acquired in adult life, usually through acquired damage to the pituitary-hypothalamic region caused by TBI.

Post TBI hormonal deficiency syndrome is typically associated with severe head traumas with a Glasgow Coma Score of less than 7 or 8 with loss of consciousness and coma. Survivors of such head trauma often suffer from impairment of cognition, language, and mood, as well as physical functioning. However, more recent research suggests that relatively mild trauma can be enough to cause a TBI and post TBI hormonal deficiency.

Motor vehicle accidents and sports, such as boxing, martial arts, wrestling, football, are common causes of TBI. As are slips and falls, blunt trauma, and shaken trauma. Even seemingly innocuous rides at amusement parks can be violent enough to cause jarring of the stock of the pituitary that can predispose us to TBI.

Kelly _et al_ found that chronic GH deficiency develops in approximately 18% of patients with complicated mild, moderate, or severe TBI, and is associated with depression and diminished quality of life. Whilst Powner _et al_ found that chronic hormone deficiency occurs in 30-40% of patients after TBI, with 10-15% of patients having more than one deficiency. Like Kelly, Powner found that 15-20% of TBI patients go on to develop GH deficiency. Results of the study by Powner _et al_ also showed that 15% of TBI patients develop gonadal hormone deficiencies and 10-30% develop hypothyroidism. The researchers found that chronic adrenal failure is widespread amongst TBI patients and that nearly a third have elevated prolactin levels.
Aimaretti et al found that GH deficiency and secondary hypogonadism were the most common acquired pituitary defects induced by TBI in the transition phase (pediatric to adolescent). The results of this study suggest that it is extremely important to give all prepubescent children who have sustained a head injury a total hormone assessment, because that head injury may cause post TBI hormonal deficiency syndrome, which could cause a whole range of problems, including short stature, personality changes, functional disability, and problems with language skills and school skills. The most recent literature suggests that hormone levels should be determined immediately after the injury and then again a few weeks later.

Thomson et al found that post-traumatic hypogonadism is very common in the acute post-TBI phase, although most cases resolve themselves within six to twelve months. However, results of this study also showed that hypogonadism persists in 10 to 17% of long-term survivors. So, it can be seen that there is plenty of evidence in the medical literature to show that there is a clear relationship between head trauma and the development of one or multiple hormone deficiencies.

**Symptomatology**

Any brain function can be disrupted by TBI. Symptoms of post TBI hormonal deficiency syndrome include: excessive sleepiness, inattention, difficulty concentrating, impaired memory, an inability to learn new things, faulty judgment, depression, irritability, emotional outbursts, disturbed sleep, diminished libido, difficulty switching between two tasks, and slowed thinking.

**Neuropathology**

What effect do diminished hormone levels have on the brain? Firstly, the presence of adequate amounts of GH is crucial if the brain is to function correctly. This is because GH plays an important role in microtubular regeneration, lipid metabolism, and dendritic growth and regrowth. What about insulin-like growth factor (IGF-1)? IGF-1 deals with the functional use of glucose in the brain. Furthermore, Cheng et al found evidence indicating that IGF-1 depletion causes disruption in lipid and microtubule metabolism, leading to impaired neuronal, somatic, and dendritic growth.

The hippocampus is very important for memory. Research suggests that the functions mediated by GH receptors in the hippocampal area may be involved in the hormone’s action on memory and cognitive function. Furthermore, beneficial effects of GH on certain functions, including memory, mental alertness, motivation, and working capacity have been reported.

Cranston et al conducted an interesting study using PET scans to investigate the effects of GH replacement on cerebral metabolism in adults with GH deficiency. The results showed that the resting cerebral metabolic rate in adults with GH deficiency is low. However, GH replacement to physiological levels increased resting cerebral metabolism towards normal levels, thus suggesting that GH has a direct effect upon the central nervous system and cellular metabolism.

**Clinical Course**

There are three phases to post TBI hormonal deficiency syndrome: the acute phase, the recovery phase, and the chronic phase. Schneider et al studied the prevalence of anterior pituitary insufficiency 3 and 12-months after TBI. Results showed that found that 56% of TBI patients had anterior pituitary insufficiency at 3 months. By 12-months this had dropped to 36%. However, GH deficiency actually increased over that period from 9% to 10%. Leah-Cerro et al conducted a similar study investigating the prevalence of TBI-mediated hypopituitarism in patients who had sustained a severe TBI within the last five years. Results showed that 17% were suffering from gonadotrophin deficiency, 6.4% were suffering from adrenocorticotrophic (ACTH) deficiency, 5.8% were suffering from thyroid stimulating hormone (TSH) deficiency, and 1.7% developed diabetes insipidus. Overall, 24.7% of participants developed some type of pituitary hormone deficiency.

Koponen et al conducted a 30-year follow-up study on patients who had suffered TBI to determine the occurrence of psychiatric disorders. Their results showed that 48.3% of study participants had had an axis I disorder that began after TBI. The most common disorders after TBI were: major depression (26.7%), alcohol abuse or dependence (11.7%), panic disorder (8.3%), specific phobia (8.3%), and psychotic disorders. Nearly a quarter (23.3%) developed at least one personality disorder. These findings led the researchers to conclude: "The results suggest that traumatic brain injury may cause decades-lasting vulnerability to psychiatric illness in some individuals. Traumatic brain injury seems
to make patients particularly susceptible to depressive episodes, delusional disorder, and personality disturbances. The high rate of psychiatric disorders found in this study emphasizes the importance of psychiatric follow-up after traumatic brain injury.”

The ER doctors and the neurologists, the very people who are responsible for the care of people with TBI, are seemingly doing nothing about the problems associated with TBI. The real key to treating these problems is hormone replacement. Aimaretti and Ghigo suggested that patients with TBI-induced hypopituitarism might benefit from appropriate hormone replacement therapy, such as anti-diuretic hormone (ADH), glucocorticoid, and thyroid hormones. They also wrote that gonadal and recombinant human GH (rhGH) replacement therapy should be given if deficiencies are found.

**Diagnosis and Treatment of Post TBI Hormonal Deficiency Syndrome**

The first and foremost thing to do in order to diagnose, or rule out, post TBI hormonal deficiency syndrome is evaluate the patient – regardless of their age. Many of the patients that I see cannot even remember sustaining a head injury, because they were two or three when they were dropped on their head or when they accidentally banged their head on the wall and ended up in the emergency room. Remember, even very mild head injuries can have their consequences – they may be subtle but they are also long-term consequences.

To evaluate patients you should perform a full hormonal assessment via a spot or 24-hour urine test for hormones and their metabolites, or serum testing. These are the most accurate and reliable testing formats for TBI. Salivary testing is not recommended for TBI. It is also important to test for neuro-endocrine markers. This can be done with either spot or 24-hour urine testing. It is important to use a laboratory with neurotransmitter expertise.

In order to treat post TBI hormonal deficiency syndrome it is necessary to identify the hormonal deficiencies present and then begin the process of replenishing the deficient hormones. Important points to remember when you suspect that a patient may have post TBI hormonal deficiency syndrome include:

- It is vital not to use the intensity of the trauma to predict the onset of post TBI hormonal deficiency syndrome – even the most subtle injuries can sometimes be enough to cause a TBI.
- It is vital that you perform hormonal testing immediately after the precipitating event to establish a baseline.
- Do not use age as a predictor. Even in a 45-year-old patient it is vital to enquire about any historical head trauma – even head trauma that occurred in their childhood.
- Although GH cannot be used at present for the treatment of TBI, it can still be used to treat adult GH deficiency syndrome. However, being aware of the etiology of such a deficiency is extremely important because you may well need to adopt a totally different approach to a patient’s treatment.
- Consider early hormonal supplementation to minimize the physical and psychological sequelae.
- Hormonal assessments can be done at three-month intervals from the date of injury, or more frequently based upon treatment.

**CONCLUDING REMARKS**

For 40 years researchers have been looking at what they can do to help people with TBI, each and every one of these studies was futile because nothing they came up with helped. They tried a whole gambit of drugs and nothing worked. Even now, few people are aware of the existence of post TBI hormonal deficiency syndrome, which means that it is down to anti-aging physicians to intervene and once again be at the cutting edge of medicine. It is up to us to educate our fellow physicians about post TBI hormonal deficiency syndrome and how to treat it.

**REFERENCES**


ABOUT THE AUTHOR

After 14 years of clinical orthopedics and 20 years as a residency trained board certified family physician, Dr. Mark Gordon integrates anti-aging medical theories into a program of sports rehabilitation. Using nutrition, exercise and his knowledge of supplementation he has helped a number of injured patients return to their activities in a significantly reduced time. Pre-operative programs help surgical outcome and reduce the down time for both sports and non-sports related injuries. Many natural products are available to accomplish these goals. Dr. Mark Gordon has been recognized as a leader in the area of anti-aging medicine and holds associate clinical professorships at USC and UCLA. Dr. Gordon has recently been reappointed as Medical Director for CBS Studios, and Medical Consultant to HBO and FX. In these positions he is available for consultation on areas of preventive, anti-aging and alternative medicine. He writes articles on nutritional supplementation and hormonal replacement, some of which have been published in Max Muscle and Planet Muscle.