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A Review of the Relationship between Mild Traumatic Brain Injury, Post-Traumatic Stress Disorder, and Temporomandibular Disorder

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Abstract

Mild traumatic brain injuries (MTBI) and the development of post-traumatic stress disorder (PTSD) have become the signature injuries of those returning from the Middle East theatre of conflict. PTSD, MTBI, and temporomandibular disorders (TMD) are statistically associated and share many common symptoms including depression and myofascial pain.

PTSD, MTBI, and TMD also share physiological and neurochemical similarities including NMDA receptor site activation. A chemical cascade follows a MTBI, releasing excessive neurotransmitters, causing secondary injury, central sensitization, and alteration of the HPA axis. PTSD is accompanied by physiological changes within the brain including HPA axis alteration, central sensitization, increased neurotransmitter sensitivity, and neuroplastic changes.

Chronic TMD patients may also suffer from central sensitization and altered HPA axis function. Measurable physiologic parameters for HPA axis and sympathetic/parasympathetic autonomic balance include heart rate variability and salivary cortisol.

With increasing numbers of war veterans returning to the United States suffering the effects of PTSD, MTBI, and TMD, providers need to be aware of the common underlying processes when faced with identically presenting patients.

Keywords: Mild traumatic brain injury; Post-traumatic stress disorder; Temporomandibular disorder; Heart rate variability; Salivary cortisol; HPA axis.

Introduction

The trigeminal nerve innervates more diverse structures than any other cranial nerve. For example, all three divisions innervate the anterior and middle portions of the dura mater, responsible for sensory innervations to the brain. The first division innervates the cornea. The second division innervates the mucous membrane of the nasal cavity, while the third division carries sensory information from the anterior two-thirds of the tongue.

The trigeminal nerve is also a structurally complex cranial nerve with both sensory and motor roots. Trigeminal sensory nuclei receive significant cervical input and one sub-nuclei may modulate another [1]. Second order neurons from the trigeminal sensory nuclei project to the thalamus [2,3] (the main pain-gating structure), and communicate with the amygdale [4] and other limbic structures [5] responsible for the emotional affect of pain [6].

Excessive stimulation of trigeminal primary afferent neurons may result in a variety of effects such as the expansion of their receptive fields [7]. Chronic excitation of second order, wide dynamic range neurons may lead to summation [8] (wind-up) and excito-toxic effects possibly causing the failure of nociceptive modulating inter-neurons [9]. The nociceptive barrage finally reaches the cortex where we become acutely aware of pain. Trigeminal pain has a large cortical representation and is therefore something that we pay attention to immediately.

A temporomandibular disorder (TMD) diagnosis is a trigeminal diagnosis with muscle, bone, joint, neurological and emotional components. TMD sufferers may have altered HPA axes [10], effecting nociception. Cortical and limbic factors modify nociception and the sensation of pain.

Two conditions that have been the subjects of recent intense research are post-traumatic stress disorder (PTSD) and mild-traumatic brain injury (MTBI). The first alters biochemical responses to stress mediated through the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis forms a negative feedback cycle regulating the homeostatic response to stress [11]. The second produces both a physical and biochemical alteration of brain function. Chronic TMD symptoms are strikingly similar to those accompanying PTSD, and MTBI.

Statistical associations between PTSD & TMD, MTBI & TMD, and PTSD & MTBI do not necessarily indicate cause-and-effect relationships. Research, however, provides increasing evidence for causal linkages serving as a reminder of the extensive interconnections between our brain centers.

Mild Traumatic Brain Injury

A traumatic brain injury is an acceleration/deceleration injury in which compression of the brain and dura into the cranium occurs. Frequently termed a concussion, they are typically the result of a motor vehicle accident, a sports mishap, or a recreational accident [12]. Recently, however, many traumatic brain injuries, mild or otherwise, have been the consequence of military activities.

Traumatic brain injuries from concussive forces are the signature injuries from the conflicts in Iraq and Aftganistan [13,14]. Nearly 30% of all patients seen at Walter Reed Army Medical Center from 2003-2005 sustained a traumatic brain injury of some kind. The proportion of all troops who sustained a MTBI has been estimated to be as high as 18% [15].

Traumatic brain injuries are classified as mild, moderate, or severe. The classification depends upon loss of consciousness, the extent of post-traumatic amnesia, and an assessment using the Glasgow Coma Scale following the injury [16]. Brain injuries accompanied by a fracture or intracranial bleeding are not defined as mild and require imaging studies. Symptoms resulting from moderate or severe injuries may not become apparent for some time and include: worsening headache, slurred speech, unequal papillary dilation, nausea, and seizures.

MTBI are concussive injuries. The severity of a MTBI may be graded by a number of scales. In general, there are 3 grades of injury [17]:

1. Grade I – no loss of consciousness, confusion or post-taumatic amnesia lasting less than 30 minutes (15 minutes in some scales).
2. Grade II – no loss of consciousness, confusion or post-traumatic amnesia lasting greater than 30 minutes (15 minutes in some scales).
3. Grade III – Any loss of consciousness.

A MTBI of any grade can alter brain physiology. These injuries may cause biochemical changes on cell membranes and synapses [18]. Post-injury, there is an immediate reduction of cerebral blood flow and an imbalance of ions across glial cell membranes [19]. There is a large release of excitory neurotransmitters including glutamate [20], dopamine, norepinephrine, and serotonin, activating N-methyl D aspartate (NMDA) receptor sites in the brain and spinal cord. These changes contribute to further biochemical injury [21-23] and excito-toxic effects [24].

Alterations in glutamate levels within the brain have been linked to depression [25,26]. Additional injurious effects include: lactic acid buildup, mitochondrial dysfunction, a reduction in intracellular magnesium, and compromised inhibition of the hippocampus [27].

The majority of MTBI symptoms resolve within several weeks. Studies show that certain symptoms may persist such as headache, dizziness, fatigue, anxiety, hyper-vigilance, and irritability [28]. This cluster of lingering post-injury symptoms have been termed post-concussion syndrome and may be present in 40-80% of MTBI patients [29]. The diagnosis may be entertained for symptoms lasting more than 3 months [30]. Presently there is no universally recognized protocol to treat MTBIs besides supportive measures.

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a specific type of anxiety disorder that may develop from exposure to one or more physically, psychologically, or emotionally terrifying events that pose a threat to an individual or another. Examples of those events include: sexual and physical abuse as a child, MVAs, abduction, emotional abuse, first responders at a casualty scene, and war experience. Not everyone exposed to traumatic events develops PTSD and symptoms usually resolve within weeks. Specific symptoms that exist for more than one month are cause for concern. Studies on troops returning from the Middle East have shown a rise in PTSD to 46% in 2007, bringing the 5-year total to nearly 40,000 with persistent symptoms [31].

More than merely a psychological effect, PTSD involves a complex set of genetic and neurochemical changes in the brain. Studies have shown that stress related genetic mutations within the central nervous system from traumatic child abuse predisposes adults to the development of PTSD [32,33]. In the normal fight-or-flight reaction to stress, catecholamines and cortisol brain blood levels are elevated briefly. In individuals experiencing PTSD, catecholamine levels are low and corticotropin releasing factor levels are elevated for a prolonged period. In addition, norepinephrine levels remain high. These findings suggest an alteration in the hypothalamic-pituitary-adrenal (HPA) axis, responsible for the homeostatic response to stress [34,35], creating a maladaptive, over-reaction. There may be a constant hyper-arousal of the amygdala (responsible for the development of emotional memories) in PTSD sufferers even in the acute phase [36], and an increased response to the neurotransmitter glutamate [37,38].

There are genetic links for a pre-disposition towards PTSD. In a study of twins exposed to combat, monozygotic (identical) twins were strongly associated with PTSD compared to dizygotic (non-identical) twins [39]. In addition, a common genetic variation of a serotonin transporter gene leads to an increased number of neurons in the thalamus. People who inherit two short-type 5-HTTLPR alleles are predisposed to depression, PTSD, and suicide [40]. The central nervous system production of the stress-induced gene *c-fos* has been shown to be greater in females than males, perhaps indicating a sex-related vulnerability to stress-related disorders [41].

The diagnosis of PTSD is based on the Diagnostic and Statistical Manual of Mental Disorders-IV [42]. There are six general categories:

1. Exposure to a traumatic event(s) of a type that is outside the range of normal human experience and would cause symptoms of distress in almost everyone.
2. Persistent re-experience of the event(s).
3. Avoidance of stimuli associated with the trauma.
4. Increased arousal symptoms. (ie insomnia, hyper-vigilance)
5. Duration of symptoms for more than 1 month.
6. Social impact of symptoms. (relationships, work, enjoyment of activities)
7. Treatment protocols for PTSD are under constant revision. One current protocol combines cognitive therapy, group therapy, desensitization, and the use of pharmacological agents such as SSRIs, SNRIs, and beta-blockers.

PTSD and TMD

Chronic TMD symptoms involve the activation of second order neurons and limbic structures within the brain. PTSD involves the activation of these same brain centers. A link between the two disorders is well established [43,44]. Two studies linked war veterans suffering from PTSD with both TMD symptoms and headache, finding that 48% of PTSD sufferers also exhibited myofascial pain symptoms [45,46]. deLeeuw and Bertoli found that, over a 5-year period, 1 in 6 patients with chronic oro-facial pain also suffered PTSD symptoms using the DSM-IV standards [47].

The physiological linkage between the two may be the result of HPA axis dysregulation present in both conditions [48,49]. Exaggerated emotions present in many PTSD patients: fear, anger, worry, and sadness, are also linked to chronic and severe pain [50]. Emotional centers influence cells in the hypothalamus that release corticotropin releasing hormone, effecting hormone synthesis in the pituitary. Chronic pain conditions also produce stressors effecting hormone release [51]. Research also suggests a link between memory, long-term pain, and central sensitization [52].

MTBI and TMD

A relationship between MTBI and TMD has been established primarily through motor vehicle accidents and sports injury data. An acceleration/deceleration injury to the brain may affect the supporting cervical neck muscle, often termed "whiplash".The concussive force injuries suffered by troops in the Middle East often have the same result. As excessive and sustained cervical nociceptive input reaches the trigeminal sencory nuclei, second order neuronal wind-up occurs and consequently central sensitization. Referred pain may be felt in the facial region. This is c common and well known phenomenon [53]. The activation of N-methyl D-aspartate (NMDA) receptors [54] triggered by excessive glutamate release from brain trauma with subsequent central sensitization [55] is common to both MTBI and TMD conditions.

MTBI and PTSD

The relationship between PTSD and MTBI is the subject of intense scrutiny. One study found that post-concussive symptoms were more prevalent in MTBI patients who later developed symptoms of PTSD [56]. Two investigations suggested that psychological factors may account for many of the MTBI symptoms and that treatment programs for MTBI should include assessments and treatment for PTSD [56,57].

The New England Journal of Medicine reported in 2008 that of 2525 U.S. Army infantry soldiers returning from the Middle East, 124 sustained MTBIs with loss of consciousness (grade 3), 260 had altered mental status (grades 1 and 2), and 435 received other injuries. 44% of those sustaining grade 3 injuries met the diagnostic criteria for PTSD. The rate of PTSD was 27% for grade 1 and 2 injuries and 16% for those with other injuries. The results revealed a strong association between MTBI and PTSD [58].

The physiological underpinnings of PTSD involve a heightened response from the amygdala and impaired regulation by the prefrontal cortex [59] as well as alterations of the HPA axis [60]. Those of MTBI involve the excessive release of glutamate, the excitory neurotransmitter linked to depression and the up-regulation of nociception. Glutamate has been found to be a direct activator of the HPA axis [61-63]. In addition, the post-injury release of dopamine, norepinephrine, and serotonin64 are neurotransmitters that regulate the HPA axis, are found to be dysfunctional in individuals suffering from both PTSD and chronic TMD pain.

Heart Rate Variability

A balance between sympathetic and parasympathetic tone is a factor in maintaining cardiac rhythm. In healthy individuals there are small differences between each heartbeat, termed heart rate variability [65]. These differences can be measured and lend insight into allostatic load and the HPA axis [66].

Patients suffering fromPTSD have a lower heart rate variability compared to non-PTSD individuals [67,68]. Low heart rate variability has also been linked to depression [69,70]. A low heart rate variability is one indicator that an individual may be less able to mount an effective stress response.

Heart rate variability is also affected by serotonin and pain perception. Heart rate variability returned to normal in a cohort of PTSD sufferers after treatment with fluoxetine68. In another study, reduced heart rate variability found in chronic pain patients, returned to normal following the relief of pain [71].

Cortisol

Cortisol is produce by the zona fasciculate of the adrenal cortex. It is the primary negative feedback hormone affecting the hypothalamus and HPA axis. Normal blood serum cortisol levels exhibit a diurnal variation, with the highest levels present in the early morning. Abnormal patterns of serum cortisol have been observed in cases of depression and psychological stress [72]. Excessive blood serum cortisol can weaken the immune system exerting a negative effect on the production of interleukin-173. Alterations in blood serum cortisol have been linked to PTSD in post-war veterans [74].

Cortisol is a measurable link to stress and regulatory function. There are several techniques to measure cortisol: blood chemistry, urinary levels, and salivary levels. Salivary measurements have been found to be most reflective of both total blood plasma cortisol [75] and plasma free cortisol [76]. It is convenient from a risk, time, and coast perspective and may be an accurate measure of HPA axis stress and allostatic load [77].

Conclusion

Our body's brain centers are interdependent. An alteration in form or function in one center is likely to cause a cascade of changes in another [78]. Co-morbid symptoms exist between PTSD, TMD, and MTBI because of common underlying physiological and neurochemical mechanisms.

Cognitive (supra-spinal) and emotional centers exert strong influences on the perception of pain [79] present in all three conditions. Distraction leads to a reduction of nociceptive brain activity in the dorsal horn80. A negative affect has been shown to increase pain perception [81,82].

With increasing numbers of war veterans returning to the United States suffering the effects of PTSD, MTBI, an TMD, providers need to be aware of the common underlying processes when faced with identically presenting patients. The Rand Corporation has estimated the costs to treat a single MTBI case for one-year at $32,000. The two-year cost for a single PTSD case varies between $6,000 and $25,000.

A study investigating the relationship between these three conditions using heart rate variability and salivary cortisol as a measure of parasympathetic function would be interesting. The SCL-90 symptom checklist is a common instrument used in studies on various pain topics to assess pain.A cohort of pre and post deployment using salivary cortisol and heart rate variability may yield information on the susceptibility to PTSD and TMD conditions.

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