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Heart rate variability and serum level of insulin-like growth factor-1 are correlated with symptoms of emotional disorders in patients suffering a mild traumatic brain injury

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HIGHLIGHTS

- Reduced heart rate variability (HRV) was noted in patients with mild traumatic brain injury (mTBI).
- The power spectrum of HRV was positively correlated with serum levels of IGF-1 in mTBI patients.
- Early HRV can be noninvasively measured to assess anxiety and depression symptoms in mTBI patients.

ABSTRACT

Objective: Patients who have experienced a mild traumatic brain injury (mTBI) are susceptible to symptoms of anxiety or depression. To explore the potential biomarkers for emotional disorders in mTBI patients, we analyzed the frequency domain of heart rate variability (HRV) and serum concentrations of four neurohormones.
Methods: We assessed mTBI patients on their first visit and follow-up. Symptoms were evaluated by the Beck Anxiety Inventory and the Beck Depression Inventory, respectively. Serum levels of adrenocorticotropic hormone (ACTH), melatonin, cortisol, and insulin-like growth factor (IGF)-1 and HRV follow-ups were measured and compared.
Results: mTBI patients were more vulnerable to symptoms of anxiety or depression than healthy controls. Reduced HRV was noted in mTBI patients compared to healthy controls. The mTBI patients demonstrated higher serum levels of ACTH, lower IGF-1 compared to healthy controls. In correlation analysis, only IGF-1 was positively correlated with HRV in mTBI patients. Both HRV and IGF-1 were correlated with symptom of depression while only HRV was correlated with symptom of anxiety in mTBI patients.
Conclusions: We infer that HRV may be more significantly correlated with emotional disorders than is IGF-1 in mTBI patients.
Significance: The study is relevant for specific diagnostic markers in mTBI patients.

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1. Introduction

Traumatic brain injuries (TBIs) are a leading cause of death and disability worldwide. TBIs are classified into three categories of mild, moderate, and severe. The most widely accepted criteria for defining mild TBI (mTBI) are (1) nonpenetrating head trauma resulting in loss of consciousness (LOC) < 30 min in duration, (2) posttraumatic amnesia (PTA) < 24 h in duration, and (3) a Glasgow Coma Scale (GCS) score of 13–15 upon acute medical evaluation (Arciniegas and Silver, 2001; Carroll et al., 2004). Unlike the explosion or sports injuries, traffic accident in Taiwan has been the major cause of TBI (69.4%), followed by falls and assaults. Motorcyclists account for the vast majority of TBI victims among traffic accidents (64.5%). Since the helmet law for motorcyclists passed in 1986, the numbers of moderate to severe TBI decreased, but that of mild TBI increased (Chiu et al., 1997). According to the recent data, 79.5% of TBI patients in Taiwan were considered mild, 8.9% moderate, and 11.6% severe (Chiu et al., 2007).

The term 'emotional disorders' is not a clearly defined medical term, but is commonly used to refer to psychological disorders (e.g., generalized anxiety disorders and major depressive disorders) that appear to affect the emotions. 'Emotional disorders' in this study refers to the symptoms of anxiety and depression. Patients who have experienced an mTBI are susceptible to emotional disorders (Silverberg et al., 2014). A significant relationship between mTBI and anxiety disorders was observed in a retrospective study (Larrabee and Rohling, 2013). A relationship between depression and mTBI has garnered increasing attention because an mTBI (i.e., concussion) resulting from blast explosions may cause long-term depression in soldiers from Iraq War (Hoge et al., 2008). In addition, retired football players with prior concussions were 3-times more likely to be diagnosed with depression (Guskiewicz et al., 2007).

The traditional evaluation of TBI remains heavily dependent on neurological and radiographic studies (Sharma and Laskowitz, 2012). However, conventional neuroimaging techniques have limited sensitivity in detecting physiological alterations caused by mTBI and are typically not used to assess the efficacy of mTBI treatments. mTBI can be difficult to detect because it is often not visible on conventional acute MRI or CT scans (Jeter et al., 2013; Yuh et al., 2014; Huang et al., 2015). The CT and conventional MRI scans of most mTBI patients in the emergency department do not reveal abnormalities (Belanger et al., 2007). The immediate challenge for emergency department physicians is to identify intracranial abnormalities in CT- or MRI-negative patients. On the other hand, in 1996, the American Academy of Neurology highlighted the potential utility of SPECT as an investigational tool in mild TBI, but noted that the data obtained lacked sensitivity, specificity, and reliability (Assessment of brain SPECT, 1996a). Ten years on, a new review noted the status of SPECT remained largely unchanged (Lewine et al., 2007). Recently, molecular imaging techniques that involve examining functional processes within the brain, such as glucose uptake and metabolism, by using ^{18}fluorodeoxyglucose and positron emission tomography (FDG–PET) can detect changes after mTBI (Byrnes et al., 2014); however, such techniques still have limitations and biases. Hence, we did not use SPECT as an evaluation tool in this study. Ideally, a diagnostic biomarker should indicate the presence or absence of disease or injury, and more specifically, should be able to stage or classify its severity (Piazza et al., 2007). Appropriate biomarker screening may yield a more selective strategy for neuroimaging, reducing the need for numerous unnecessary imaging exams. Brain-specific proteins or hypothalamus-related neurohormones released into the bloodstream after brain injury, as a result of cellular damage and activation, have demonstrated the potential to serve as diagnostic and prognostic markers in mTBI (Dash et al., 2010). However, no clinically accepted TBI peripheral blood biomarkers are currently available (Siman et al., 2013).

There is an augmented stress response after an mTBI during the first 2 weeks post-injury (Griesbach et al., 2012). The stress causes acute activation of the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis occurs initially as a protective response to a TBI by promoting intravascular fluid retention and elevating cortisol levels (Griesbach et al., 2012). Both human and animal studies suggested that HPA axis dysregulation is associated with negative mood states (Vreeburg et al., 2009) or endocrine dysregulation (Posener et al., 2000). For example, hypopituitarism was reported to occur in 35–80% of patients in rehabilitation centers following a TBI (Mirzaie et al., 2013), with adrenal insufficiency accounting for approximately 30–50% of those cases (Llompart-Pou et al., 2010a). In patients with mild or moderate TBI, adrenocorticotropic hormone (ACTH) deficiencies may improve over a 5-year period. However in severe TBI, the ACTH status of patients at the 1st-year evaluation persisted at the 5th year (Tanriverdi et al., 2013). Besides ACTH, cortisol is produced by the zona fasciculata of the adrenal cortex, is released in response to stress, and is a so-called "stress hormone". Significant increases in 7-day cortisol levels of 31 TBI survivors was reported (Cernak et al., 1999). Circadian variability of cortisol in the serum was proven to be disturbed in TBI patients (Llompart-Pou et al., 2010b). There are no studies examining the relationship of cortisol variations with neurological outcomes in mTBI patients. Thus, it is crucial to monitor serum neurohormones, including ACTH and cortisol, during the post-traumatic period.

Hypopituitarism was reported to occur in mTBI patients in rehabilitation centers (Mirzaie et al., 2013). Hypopituitarism is a clinical syndrome characterized by deficiency in pituitary hormone production and may result from disorders involving the pituitary gland, hypothalamus, or surrounding structures. Missed or delayed diagnosis of hypopituitarism can lead to permanent disability or death (Fernandez-Rodriguez et al., 2015). Therefore, monitoring pituitary functions after TBI over time is important, especially in patients with an mTBI. Traditionally, insulin-like growth factor (IGF)-1 is measured to help evaluate pituitary function such as diagnosing the cause of growth abnormalities, and monitoring treatment of growth hormone (GH) deficiencies and excesses (Popovic, 2005). IGF-1 is a hormone similar in molecular structure to insulin. Recently, studies indicated that serum IGF-1 levels decreased in both the early and late periods after a TBI (Ozdemir et al., 2012). Decreased levels of serum IGF-1 were correlated with hippocampal neuron loss and spatial memory deficits. Circulating IGF-1 levels may be predictive of cognitive dysfunction resulting from hippocampal damage following a traumatic injury (Ozdemir et al., 2012). Although IGF-1 is viewed as a potential neuroprotective treatment for TBI-induced damage (Rubovitch et al., 2010), it is still unclear whether the serum concentration predicts the outcome of an mTBI. In our study, we also considered IGF-1 as a candidate biomarker for mTBI.

In addition, sleep disturbances occur in patients with mTBI (Ma et al., 2014). A study showed that the circadian rhythm is fundamentally disturbed in patients with anxiety or depression (Srinivasan et al., 2009), and early-morning awakening is a prominent symptom of clinical depression (Germain and Kupfer, 2008), suggesting a close link between the melatonergic system and anxiety (Srinivasan et al., 2009) or depressed mood (Pandi-Perumal et al., 2009; Malhi and Kuiper, 2013). Melatonin, secreted nocturnally by the pineal gland, is an endogenous sleep regulator (Lemoine and Zisapel, 2012). A randomized, double-blind, placebo-controlled trial by Hansen et al indicated melatonin significantly reduced the risk of symptoms of depression and anxiety in women (Hansen et al., 2014). Although impaired melatonin production and complaints of poor sleep quality are common in the

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