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A review of the neuro- and systemic inflammatory responses in post concussion symptoms: Introduction of the "post-inflammatory brain syndrome" PIBS

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ABSTRACT

Post-concussion syndrome is an aggregate of symptoms that commonly present together after head injury. These symptoms, depending on definition, include headaches, dizziness, neuropsychiatric symptoms, and cognitive impairment. However, these symptoms are common, occurring frequently in non-head injured controls, leading some to question the existence of post-concussion syndrome as a unique syndrome. Therefore, some have attempted to explain post-concussion symptoms as post-traumatic stress disorder, as they share many similar symptoms and post-traumatic stress disorder does not require head injury. This explanation falls short as patients with post-concussion syndrome do not necessarily experience many key symptoms of post-traumatic stress disorder. Therefore, other explanations must be sought to explain the prevalence of post-concussion like symptoms in non-head injury patients. Many of the situations in which post-concussion syndrome like symptoms may be experienced such as infection and post-surgery are associated with systemic inflammatory responses, and even neuroinflammation. Post-concussion syndrome itself has a significant neuroinflammatory component. In this review we examine the evidence of neuroinflammation in post-concussion syndrome and the potential role systemic inflammation plays in post-concussion syndrome like symptoms. We conclude that given the overlap between these conditions and the role of inflammation in their etiologies, a new term, post-inflammatory brain syndromes (PIBS), is necessary to describe the common outcomes of many different inflammatory insults. The concept of post-concussion syndrome is in its evolution therefore, the new term post-inflammatory brain syndromes provides a better understanding of etiology of its wide-array of symptoms and the wide array of conditions they can be seen in.

Abbreviations: PCS, post-concussion syndrome; mTBI, mild traumatic brain injury; TBI, traumatic brain injury; RA, rheumatoid arthritis; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5; ICD-10, International Classification of Diseases 10; CT, computed tomography; MRI, magnetic resonance imaging; PTSD, post-traumatic stress disorder; Il-6, Interleukin 6; Il-1β, Interleukin 1β; Il-1α, Interleukin 1α; Il-1ra, Interleukin 1 receptor antagonist; Il-2, Interleukin 2; Il-8, Interleukin 8; Il-10, Interleukin 10; Il-12, Interleukin 12; TNF-α, Tumor Necrosis Factor α; IFN-α, Interferon α; IFN-β, Interferon β; IFN-γ, Interferon γ; CRP, C-reactive protein; mRNA, messenger ribonucleic acid; SIRS, systemic inflammatory response syndrome; MODS, multi-organ dysfunction syndrome; CSF, cerebrospinal fluid; LPS, lipopolysaccharide; COX-2, cyclooxygenase 2; REM, rapid eye movement; HIV, human immunodeficiency virus; HPA, hypothalamic-pituitary-adrenal; CFS, chronic fatigue syndrome; TLR-4, Toll-like receptor 4; ACTH, adrenocorticotropic hormone; MCP-1, monocyte chemoattractant protein 1; POCD, post-operative cognitive dysfunction; PIBS, post-inflammatory brain syndromes; DAI, diffuse axonal injury; PCD, postconcussional disorder.

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1. Introduction

1.1. Introduction

Post-concussion syndrome (PCS) revolves primarily around an aggregate of symptoms presenting after head injury. These symptoms include headaches, dizziness, neuropsychiatric symptoms, and cognitive impairment (Bazarian et al., 1999). Although the current definitions of PCS focus on head injury (American Psychiatric Association. Task Force on DSM-IV, 2000; World Health Organization (WHO), 2009), similar symptoms also appear after whiplash injuries (Haas, 1996). Perhaps more startling, a number of studies have compared patients with mild traumatic brain injury (mTBI) to controls without a history of head injury and found a high prevalence of the same symptoms in both groups (Gouvier et al., 1988; Gunstad and Suhr, 2004). In a landmark paper, Meares et al. (2008) studied patients with systemic poly-trauma (multiple traumatic injuries to areas of the body other than the head) as well as patients with mTBI and reported that patients need not sustain a brain injury to present with the same symptoms as those seen in PCS. These findings held up in their further study in 2011 (Meares et al., 2011). After reviewing all available high quality evidence, The International Collaboration on Mild Traumatic Brain Injury Prognosis concluded that that PCS was not specific to mTBI and recommended "that the term postconcussion syndrome be replaced with posttraumatic symptoms because they are common to all injuries" (Cassidy et al., 2014). This has led us to question the possible mechanisms linking systemic injury and PCS like symptoms. Traditionally the mechanism of post-concussion symptoms was attributed to diffuse mechanical injury to nerve cells such as diffuse axonal injury (DAI), caused by the shear stress and tissue deformation in head trauma (Maruta et al., 2010). In this paper, we will review the evidence supporting the possibility that mechanisms other than direct mechanical disruption of neurons are responsible for PCS. More particularly, we will consider evidence linking PCS symptoms with systemic inflammatory and immune responses. We consider both experimental evidence and evidence of correlation.

1.2. Definition of PCS

There are currently two definitions used to describe PCS: one is given by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the other by the International Classification of Diseases (ICD-10). The application of the criteria in each of these definitions yields widely different results within the same patient population (McCauley et al., 2005). The DSM-IV definition of post-concussional disorder (PCD) requires a history of head trauma leading to significant cerebral concussion, abnormalities on neuropsychiatric testing or quantified cognitive assessment of attention or memory deficits and three or more of the following symptoms lasting at least 3 months: (1) becoming fatigued easily, (2) disordered sleep, (3) headache, (4) vertigo or dizziness, (5) irritability or aggression on little or no provocation, (6) anxiety, depression, or affective lability, (7) changes in personality (e.g., social or sexual inappropriateness), (8) apathy or lack of spontaneity. These symptoms cannot be explained by any other mental disorder and must result in a decline in functioning for a diagnosis to be made (American Psychiatric Association. Task Force on DSM-IV, 2000). The ICD-10 definition, meanwhile, requires three of the following symptoms: headache, dizziness, fatigue, irritability, insomnia, concentration and performing mental tasks, impairment of memory and intolerance to stress, emotional excitement or alcohol after head trauma (World Health Organization (WHO), 2009). The DSM-5 lacks a definition of PCS. However, it does contain the diagnosis major or minor neurocognitive disorder due to traumatic brain injury (TBI) (American Psychiatric Association. Task Force on DSM-IV, 2013). Similar to the DSM-IV definition of PCD, the DSM-5 focuses on neurocognitive deficits. It requires evidence of both a traumatic brain injury and neurocognitive deficits, as well as the temporal correlation of these two factors. Other post-concussion symptoms are mentioned as being possibly associated but are no longer diagnostic criteria. For the purposes of this paper, we examine the symptoms from both the ICD-10 and DSM-IV definitions in order to be complete.

1.3. Etiologies of post-concussion syndrome

Research into the cause of PCS has focused primarily on two mechanisms: physical injury to the brain and the psychosocial impact of the mTBI. mTBI is frequently associated with an absence of intracranial abnormality on conventional computed tomography (CT) and magnetic resonance imaging (MRI) – even in patients reporting PCS symptoms such as poor memory and concentration, headache, dizziness, depression and irritability (Carroll et al., 2004; NA, 1993). This suggests that the cause of PCS must either be non-organic, or occur at a level too small to be visualized on conventional anatomic imaging.

1.4. The role of psychological changes

As the symptoms of PCS are similar to those of the somatization seen in psychiatric disorders such as post-traumatic stress disorder (PTSD), it has been suggested that psychological changes could be linked to the occurrence of PCS symptoms. PTSD has been described as "the complex somatic, cognitive, affective and behavioral effects of psychological trauma" (van der Kolk et al., 1996), and patients with PTSD often experience intense fear or helplessness resulting in re-experiencing, avoidance, arousal (often including sleep disturbances, irritability and outbursts of anger), and social and functional impairments (American Psychiatric Association. Task Force on DSM-IV, 2000). TBI and PTSD have high rates of co-occurrence among civilians and even more so among soldiers who suffer combat-related TBI. Eleven percent of American soldiers returning from combat in Iraq and Afghanistan were reported to screen positive for PTSD in 2008 (Halbauer et al., 2009). Among returning soldiers with mTBI, 62% screened positive for PTSD (Schneiderman et al., 2008). This would appear to provide evidence that PTSD may explain symptoms seen after mTBI. However, it must be noted that most studies on this association are in soldiers, and it is unknown if this has validity for all populations that experience mTBI (see Table 1).

A recent study by Lagarde et al. (2014) examined PTSD in the context of mTBI and found that mTBI was a predictor of PTSD but not of PCS. In addition, the symptoms of PCS grouped similarly to hyperarousal symptoms of PTSD (Lagarde et al., 2014). However, the authors used the DSM-IV PCS definition for the prediction model, rather than a more mTBI specific composite model developed in the same patient sample. Further the clustering of symptoms only aligned with the hyperarousal symptoms of PTSD and not other PTSD symptoms, which clustered differently. While some symptoms of PCS such as headache, dizziness, and sleep impairment are also seen in PTSD (American Psychiatric Association. Task Force on DSM-IV, 2000), patients with PCS lack several key symptoms seen in PTSD such as flashbacks and avoidance of triggers. In addition imaging has revealed other differences between individuals with PCS and those with PTSD. In the early stages (1–3 weeks) after mTBI, individuals who develop PCS have alterations in resting state functional MRI and have alterations in the temporal and thalamic regions, and in the frontal region 6 months

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