Chapter

Post Concussion Syndrome

Mohammad Nadir Haider and Itai Bezherano

Abstract

Post-concussion syndrome (PCS) is a complex disorder and the complete pathophysiology is still not completely understood. PCS can be subcategorized into physiological PCS, vestibulo-ocular PCS, cervicogenic PCS, and mood-related PCS based on predominant clinical signs and symptoms. Physiological PCS is the most classic type of PCS and is due to global metabolic dysfunction in the brain which affects the autonomic nervous system (ANS) and cerebral blood flow (CBF) auto-regulation. This is suspected to be the cause for symptom-limited exercise intolerance which is a characteristic finding in this subtype. In this chapter we discuss the definition of PCS and the main subtypes. We further discuss possible causes for symptoms of PCS based on research that have studied this disorder using advanced imaging, cardiovascular and cerebrovascular metrics, and intracranial pressure. Finally, we discuss the treatment of PCS and the possible long-term effects.

Keywords: mild traumatic brain injury, concussion, post-concussion syndrome, autonomic nervous system dysfunction, cervical post traumatic disorder, vestibulo-ocular post traumatic disorder, exercise treatment

1. Introduction

Concussions are defined as reversible neurological dysfunction in the absence of gross brain lesions [1], caused by either a direct blow to the head, neck, or elsewhere on the body with an impulsive force transmitted to the head [2]. Although there is some ambiguity in the definitions of mild traumatic brain injury (mTBI) and concussion, the term concussion usually refers to a milder head injury (GCS = 15) and generally used in the context of sport-related injuries while mTBI are a broader term that includes concussion [3]. Concussions have become an international public health concern and it is estimated that about 42 million people suffer from some form of mTBI every year [4]. In the US alone, it is estimated that 1.6–3.8 million mTBI occur each year [5] and approximately 5–10% of the population will experience a concussion in their lives [6]. Some populations, like military personnel, are at a higher risk for concussions and mTBI. It is estimated that approximately 19.5–22.8% of all returning deployed US troops suffer exposure to blast and/or concussive TBI [7].

The pathophysiology of concussion has been studied in great detail, yet it is one of the least understood injuries facing the neuroscience or sports medicine community [8]. It is hypothesized that acceleration/deceleration and rotational forces cause diffuse injury to the neurons, which causes an ionic imbalance and release of a cascade of neurotransmitters [9–11]. To restore homeostasis, membrane pumps become activated which results in a brief hyper-metabolic state. Lactate is produced, which further impairs neuronal function [12]. Intra-axonal alterations within in the subaxolemmal, neurofilament, and microtubular cytoskeleton

network with impairment of axonal transport as well as impaired glucose metabolism have been observed in the acute and subacute phase after mTBI, which support the hypothesis of metabolic and cellular disruptions in the brain [13].

The typical duration of clinical recovery in majority of concussions is 7–10 days, but it is estimated that 10% [14] to 30% [15] of adolescents and 10–15% [16, 17] of adults take much longer to recover. These statistics have ranged from 5% to more than 50% in the published literature; the primary cause of this variation is due to the different criteria used to measure dysfunction [18]. If symptoms persist for more than 2 weeks in adults, or 1 month in adolescents, then the diagnosis of post-concussion syndrome (PCS) is made [19]. However, this terminology is incorrect because technically it is not a *syndrome*. A *syndrome* is a consistent set of findings associated with a condition with symptom linkage and of symptom resolution [20], but currently there is no gold-standard symptom or set of symptoms that are diagnostic of PCS [21] or its recovery [22]. PCS is defined in the World Health Organization's International Classification of Disease 10 (ICD-10) as history of head trauma with or without loss of consciousness preceding at least three of the following symptoms: headache, dizziness, malaise, fatigue, noise tolerance; irritability, depression, anxiety, emotional lability; subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment; insomnia; reduced alcohol tolerance; and preoccupation with above symptoms [23].

Self-reported symptom checklist have been used to report the symptoms of a concussion, the most common being the post-concussion symptom scale (PCSS) [24]. It is a list of 22-symptoms, which can be rated on a Likert scale (no symptom to severe symptom), with a maximum possible score of 132. Unfortunately, these symptoms are not specific to concussions or PCS and the healthy population has an average score of 6 out of 132 [25], hence several studies use the cutoff of 7 on the PCSS to diagnose concussion and PCS [22]. However, there is no symptom cutoff limit that can reliably identify people with concussion and/or PCS. One study [26] showed this cutoff criterion (7 out of 132) incorrectly labeled 34% of healthy people with PCS, which is higher than people with a concussive head injury (31%). Self-reported symptom checklists have also been criticized because there is variation in symptom reporting between people. Athletes are known to under-report their symptoms, whereas people with secondary gain are known to over-report them [27]. Another potential downside of symptom checklists is that it is suggested to reinforce illness behavior and encourages over-endorsement of symptoms that might not otherwise have been reported on free recall [28, 29]. Still, this is a useful tool for clinicians because it helps track symptoms longitudinally, so it is always advised to compare symptom reports with previous ones. Another popular symptom checklist is the post-concussion symptom inventory (PCSI), it has an added benefit which allows patients to report symptoms before and after head injury which makes is easier for clinicians to interpret its findings [30].

2. Post-concussion syndrome classification

PCS have been subcategorized based on their predominant pathophysiology as shown in **Figure 1** [31, 32]. These classifications may overlap as it is possible to have one or more associated conditions after a head injury. Physiological PCS are believed to be true concussions because these patients typically present with minimal physical examination abnormalities but can have signs of oculomotor and/or vestibular dysfunction. They often complain of cognitive fatigue, headaches, and

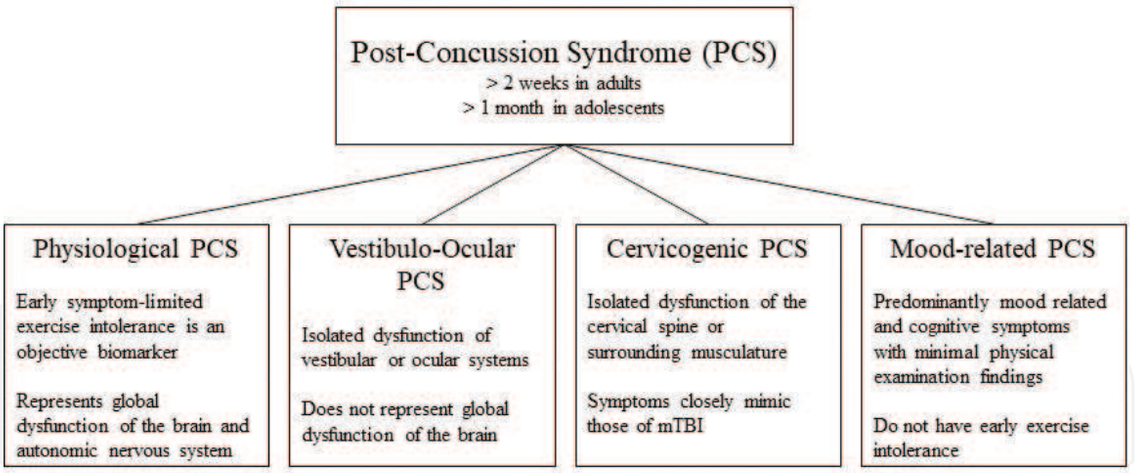

Figure 1.
Post-concussion syndrome subtypes. Classification of the different types of PCS based on predominant clinical signs and symptoms.

balance problems [33], but the most objective biomarker of physiological dysfunction is symptom-limited exercise intolerance at a low heart rate [34]. These patients have worsening of existing symptoms, or onset of new symptoms, when they begin to exercise. This exacerbation occurs at below 70% of their age appropriate maximum heart rate [32]. The pathophysiology of this type of PCS will be discussed later in more detail.

Vestibulo-ocular and cervicogenic PCS are not true concussions since they do not involve global metabolic disturbance of brain function, rather post-traumatic disorders of isolated subsystems from which the symptoms originate, i.e., the central oculomotor and vestibular systems and upper cervical spine respectively [35]. They present with predominantly vestibulo-ocular/cervical signs and symptoms, respectively, and may demonstrate exercise intolerance during graded treadmill testing, but symptom exacerbation typically occurs at a significantly greater workload (beyond 70% of age-predicted maximum heart rate) than in physiological PCS [34]. This late symptom exacerbation is thought to be due to stress on the vestibular/ocular systems or excessive motion of the cervical spine characteristic of walking/running at higher workloads. Abnormal physical examination findings that point towards a vestibular or ocular pathology, such as smooth pursuits, repetitive saccades, vestibulo-ocular reflex, near point convergence (binocular vision), abnormal accommodation (monocular vision), and benign paroxysmal positional vertigo, are present in almost 70% of patient with mTBI [36, 37]. Clinical predictors of vestibulo-ocular PCS include female sex, pre-injury depression, post-traumatic amnesia, history of motion sickness, dizziness, blurred vision, and difficulty focusing at the time of injury [38, 39]. The neck and suboccipital regions are also frequently involved in head injuries and can cause headaches, persistent dizziness, and balance difficulties [40]. Isolated persistent dysfunction (beyond the normal duration of recovery) may suggest lesions in cranial nerves, their nuclei, or the brain stem, and are associated with prolonged recovery [41]. These overlapping symptoms make the diagnosis of PCS difficult and it is possible that patients with physiological PCS can also have isolated dysfunction in the vestibular, ocular, and cervical systems at the same time.

The last subtype, mood-related PCS, presents with symptoms that are primarily affective and/or cognitive in nature, have minimal physical examination signs, and are capable of exercising to exhaustion without significant symptom exacerbation. The management of this sub-type is challenging, even for an experienced

concussion expert, because of the extensive overlap with symptoms of primary mood disorders. The most recent concussion in sport group (CISG) guidelines recommend a multidisciplinary team approach to treatment that may involve a psychiatrist, a psychologist and/or a neuropsychologist [21]. Other disorders, such as chronic post-traumatic headaches and migraines, are treated in a similar fashion and should be referred to their corresponding specialist, i.e., a neurologist.

3. Sex differences

The duration of recovery is suggested to be longer for females with males recovering in an average of 7–10 days where as females recovering in an average of 14 days [21]. Healthy females at baseline are also reported to have higher symptom severity on concussion symptom scales than healthy males [42]. A study [43] suggests that adolescent females were more likely to be diagnosed with PCS due to increased symptom load as well as the duration of symptoms because males returned to being asymptomatic by the fourth week of recovery, missing the PCS diagnostic criteria. Another study suggests the female sex to be a significant predictor of prolonged PCS, which they described as symptoms that lasted for more than 3 months [44]. Interestingly, the same study found this association to be more prominent between the ages of 14 and 56, which is characterized by drastic fluctuations of hormone levels. This calls into question the role of female sex hormones in recovery trajectories and symptom resolution. Some critics have suggested that the above theories overestimate sex effect on PCS, suggesting that the increased relative rates of females entering PCS and experiencing PCS symptoms are more often due to differing societal pressures and perceived stigma experienced by the sexes causing many males to perceive their symptoms as resolved [45, 46].

A topic of more recent research is the morphological and structural differences in females that could predict PCS. It has been well established by the literature that female athletes, given equal exposure and risk, are more likely to sustain a concussion [47]. The reasoning behind a female's increased vulnerability is still under debate, with decreased neck girth and differences in play style all seeming to play a role [48, 49]. A recently [50] identified difference in female brains is decreased axon size and density. This decreased axon size complimented with an increased density of axonal fibers could predispose females to having more severe consequences than males when given the same impact. More research in the cellular differences between males and females could address the differences observed in PCS incidence.

4. Imaging

Currently, the ICD-10 states that no advanced imaging methods can diagnose a concussion [21], but some studies have shown that certain types of PCS have observable differences from each other on advanced imaging. PCS patients with neuropsychiatric complains have significant differences than PCS patients without them. Diffusion tensor imaging (DTI) studies [51] have shown decreased fractional anisotropy (FA) in the superior longitudinal fasciculus, vermis, and white matter around the nucleus accumbens and anterior limb of the internal capsule which correlates to symptoms of depression and anxiety. A larger meta-analysis [52] showed patients who had predominantly cognitive/affective symptoms 1 month post-mTBI had significantly increased FA and reduced mean diffusivity (MD) than those with other symptoms. Increased FA indicates faster unidirectional flow within neurons and decreased MD indicates better axonal integrity [53], which is surprising after the

brain is injured. Another way to interpret these findings is that there is more activity within each neuron, which is more consistent with the hypothesized post-mTBI hyper-metabolic state described above. Long-term changes have also been shown to occur after mTBI and PCS. A study [54] that longitudinally assessed regional brain volumes at 1 month post-injury and again at 1 year post-injury. They found significant reductions in the anterior cingulate white matter, left cingulate gyrus isthmus white matter, and right precuneal gray matter. The reduction in left cingulate gyrus isthmus correlated with clinical scores on anxiety and depression, which is a prominent symptom of PCS. Similarly, electrophysiology studies have also provided evidence for this. Electroencephalographic (EEG) studies [55] have shown altered frontal-alpha asymmetry and beta asymmetry in patients who self-reported depression/anxiety and anger post-mTBI respectively. A magneto-encephalography study [56] has reported high accuracy in identifying patients with mTBI, with a much higher reliability for blast injuries. More research is warranted to identify imaging biomarkers that can diagnose mTBI, the different PCS sub-types, as well as their recovery.

5. Autonomic nervous system (ANS) dysfunction and PCS

The Autonomic Nervous System (ANS) control centers are located in the brainstem and can be damaged when rotational forces are applied to the upper cervical spine [57]. This damage has been confirmed in a recent DTI study [58] in patients with PCS, with PCS patient displaying a significantly higher percent high and low voxels upon follow up scan. The ANS dysfunction could be due to damage to these centers are/or due to uncoupling of these centers and cardiovascular system [8, 59]. This may cause reduced heart rate variability, a measure of sympathovagal reactivity. This stunted reactivity has been documented at rest and during exercise in the acute phase after concussions, as well as several months after [60]. Cardiovascular dysfunction in PCS may manifest as symptoms of orthostatic hypotension, postural orthostatic tachycardia syndrome, and altered heart rate and blood pressure responses at rest and during exercise, all which are common in PCS [31]. Studies have also shown abnormal ANS function, as assessed by heart rate variability metrics, when moving from rest to a state of increased metabolic demand in PCS, and this dysfunction can persist even after the patient is clinically recovered [61].

Patients with acute concussions and PCS have also been found to have higher rates of sympathetic nervous system output than controls, as exemplified by higher resting heart rates [62] and higher heart rates during cognitive [63] and physical exercise [64]. A study done on acutely concussed adults showed a blunted parasympathetic response to stimuli, with concussed athletes showing a stunted mean arterial pressure and first-minute high frequency power rise when compared to controls, as well as altogether lack of significant changes in heart rate upon face cooling [65]. This abnormal sympathovagal imbalance may help explain some of the clinical symptoms of PCS. One example is sleep disturbances in PCS because it involves activation of the parasympathetic drive [66]. This increased sympathetic drive may interfere with the onset and maintenance of sleep [67].

6. Cerebral blood flow and PCS

The brain needs a constant perfusion pressure, i.e., the supply of blood and nutrients, irrespective of changes in cerebral blood flow (CBF) or systemic blood pressure. Increases or decreases in CBF are detected by a series of receptors which provide local and systemic responses [68]. Local responses include constriction

or dilation of cerebral blood vessels and systemic responses include altering the cardiac contractibility and systemic blood pressure. This protects the brain from changes in sympathetic nerve activity, mean arterial blood pressure, and arterial CO_2 levels [69]. Of relevance to physiological PCS, the ANS controls the CBF response to exercise which is suspected to be the cause of symptom exacerbation on physical exertion [70]. Evidence to support this hypothesis includes lower resting global CBF detected beyond symptom recovery using MR-angiography, with 64% of sport-related concussion patients showing CBF improvements within 30 days [71, 72], and regional alterations in resting CBF in patients with PCS [73–75]. Taken together, there is an abundance of evidence that cerebral autoregulation is impaired in PCS, a likely explanation for many physiological PCS symptoms.

Functional magnetic resonance imaging (fMRI) have also been used to assess patients with concussion and PCS. fMRI can assess task-evoked blood-oxygen-level-dependent (BOLD) responses either during resting state or during cognitive tasks [76]. PCS patients have cognitive intolerance so it logical to assess for differences in activation/inactivation during cognitive tasks. Changes in regional deoxyhemoglobin concentrations can also been assessed using functional near-infrared spectroscopy (fNIRS) [77]. Abnormal CBF regulation should lead to differences in BOLD responses in the PCS brain so research is currently being done to find objective biomarkers for PCS. Unfortunately, the literature is not decisive [78]. Studies have shown decreased BOLD activity in thalamus and hypothalamus as well as frontal/temporal regions but increased functional connectivity in certain brain circuits including enhanced thalami-cortical functional connectivity based on resting-state BOLD responses in TBI patients in comparison to healthy controls. There could be several reasons for these differences, it could be due to the multiple sub-types of PCS, some causing an increases response whereas other causing a decreased response, or due to the time since injury with acute cases showing more activation due to neuro-metabolic activity and chronic cases showing decreased activity. More research is warranted to understand the pathophysiology of CBF autoregulation disturbances in PCS.

7. Intra-cranial pressure (ICP) and PCS

Intra-cranial pressure (ICP) is the pressure of the cerebrospinal fluid in the subarachnoid space and is between 7 and 15 mmHg in a healthy supine adult and -10 mmHg in the standing position [79]. Since the brain is inside a stiff skull with fixed volume, an increase in ICP could lead to impaired CBF and is an important cause of secondary insult due to ischemia [80, 81]. ICP can be measured using direct and indirect methods. Direct methods, such as intraventricular catheter, are invasive, have high risk of complications and are not justified for mTBI [82]. Indirect methods, like ultrasonographic or ophthalmological, are noninvasive but have a downside of being less sensitive and less reliable [83]. Increased ICP has already been documented in moderate and severe traumatic brain injury (TBI) and their treatment includes monitoring and normalization of the ICP. Due to the mild nature of mTBI, directly measured ICP has not been studied in much detail in this population but there is one systematic review that suggests a prolonged increase in ICP after an mTBI and recommends further research [84]. One particular study [85] of interest used intravenous hypertonic 3% saline on acutely concussed patients. Hypertonic saline is a commonly used pharmacotherapy for treatment of increased ICP and its efficacy has been documented in moderate to severe forms of TBI [81, 86–89]. The study showed a significant decrease in concussion-specific symptoms after an infusion of hypertonic saline but did not measure ICP, hence the

ICP response to hypertonic saline is an assumption. More research needs to be done in PCS to investigate this possible alternate method of treatment.

8. Neuroinflammation

Neuroinflammation is the inflammation of nervous tissue and is present in several pathological conditions such as infection, injury, autoimmunity, toxicity and aging [90]. The central nervous system (CNS) has its own native cells, the microglia and astrocytes, capable of initiating the inflammatory response [91–93]. While neuroinflammation is recognized to promote protective and regenerative effects by activating alternative pathways, persistent neuroinflammation is considered detrimental in several diseases and is an area of interest in several neurodegenerative diseases [94]. Among the several inflammatory mediators released after TBI, some of the most researched include tumor necrosis factor-α (TNFα) [95] and interleukin-1β [96]. TNFα has been shown to be produced early after experimental mTBI, generally returning to baseline levels within 24 hours of injury. Mice with dysfunctional TNFα systems have prolonged recovery (2–3 weeks versus >4 weeks), increased cell damage, and increased blood brain barrier permeability (BBB) with the extent of BBB breach being $0.9mm^3$ greater in TNFα receptor lacking mice after TBI [97, 98]. However, the literature on TNFα role in mTBI is controversial. Older studies have shown that inhibition of TNFα after mTBI in animal models can be beneficial by improving neurological outcome, motor function recovery, and decreasing edema size [99, 100]. However, a newer study has shown that TNFα knockout mice performed poorly when compared to wild type mice after concussive brain injury [101]. The authors of that study also concluded that TNFα inhibition influence cognitive deficits independent of mTBI so these therapies are not appropriate for mTBI.

9. Treatment of PCS

Treatment of concussion and PCS has changed significantly over that past decade. The previous standard of care used to be complete physical and cognitive rest with a high degree of social isolation until symptoms resolve [102]. This "rest is best" model of care was supported by evidence that showed that the brain is vulnerable immediately after a concussion with cognitive or physical stress [12] and excessing physical activity [103, 104] would prolong the recovery. Forced aerobic exercise imposed upon rodents within 2 weeks of fluid percussion-simulated concussion was shown to be detrimental to recovery of cognitive function. However, exercise administered three or more weeks after injury in rodents was beneficial to both. A recent randomized controlled trial in humans compared prolonged rest to a short period of rest followed by a step-wise return to activity and found that the strict rest group reported more daily symptoms and a prolonged duration of recovery [105]. Another observational study suggests that moderate levels of physical activity, specifically aerobic exercise, within the first week after injury reduces the incidence of PCS in children and adolescents [15]. This growing body of evidence has changed the management of concussions and PCS and the most recent CISG guidelines [21] recommend a short period of rest (24–48 hours) post-injury, followed by a graded return to sub-threshold activity. There have been more studies [106] that have shown the benefits of early sub-threshold aerobic activity in concussion and PCS since guideline came out. A recent randomized controlled trial [107] of over a hundred acutely concussed adolescents showed a significant reduction in

recovery time from a median of 17 days in the placebo group to a median of 13 days in the aerobic exercise group ($p = 0.006$). This study is a turning point and will affect the approach to concussion treatment worldwide [108].

There are several theories why light to moderate levels of exercise can improve recovery from PCS. The neurocognitive benefits of exercise, such as attenuation of cognitive impairment and reduction of dementia risk in humans, have been known for years [109]. The proposed mechanism of brain health is due to the action of factors that promote neuron growth and repair. Brain derived neurotrophic factor (BDNF) is one of these factors that increase hippocampal volume and improves spatial memory [110]. BDNF levels have been shown to increase after exercise in animals [109] which has provided pre-clinical support for the observation that patients with PPCS recover much faster with sub-threshold aerobic exercise treatment [29]. In humans, studies have shown that exercise increases BDNF level as early as 5–6 weeks after initiation of aerobic training, which has a positive influence on brain neuroplasticity [111, 112]. In regards of CBF regulation, physical deconditioning from prolonged rest has been shown to impair CBF regulation [113], which is already impaired in PCS as discussed above, whereas exercise has been shown to be beneficial in improving CBF regulation [114]. The rapidity of the beneficial effect of exercise on neuroplasticity suggests improved neuronal function rather than reduced cerebrovascular disease risk being the cause for increased brain health and function. An interesting finding is that not all light to moderate exercise causes an increase in BDNF. Rats who were "forced" to exercise after concussion did not increase BDNF levels and showed an increase in stress hormone levels, which was not seen in rats who exercised voluntarily [115, 116]. This emphasizes the benefits of voluntary, sub-symptom threshold exercise during PCS.

Currently, there are no pharmacological therapies that are recommended for PCS [117]. Several pharmacological therapies have been researched but there is not enough empirical evidence to suggest their efficacy. A randomized controlled trial [118] studied the effects of the anti-Parkinson drug, amantadine, in adolescents with PCS and found that it significantly improved symptomology and cognitive function (as assessed by a computerized neurocognitive test). However, more evidence is needed to recommend these therapies. Psychostimulants such as methylphenidate and amphetamines, have been considered as pharmacological therapies for cognitive dysfunction after PCS [117]. This is based on studies that have proven their efficacy in moderate and severe forms of TBI [119–121]. Research is required on patients with mTBI before it can be recommended for PCS.

10. Long-term sequelae

There has been an increase in the awareness of long-term consequences of repetitive concussions and PCS since the discovery of chronic traumatic encephalopathy (CTE) in a retired American football player in 2005 [122]. CTE is a neurodegenerative disorder characterized by significant emotional disturbances, cognitive decline, and deposition of Tau proteins in the brain [123]. The Tau proteinopathy seen in CTE is different from the Tau proteinopathy seen in Alzheimer's disease because it is found widespread in the frontal and temporal lobes [124], as opposed to localization in the limbic system in Alzheimer's. There is no uncertainty that CTE is caused by repetitive head injuries, and has been described as early at 1928 in boxers [125], and the increased awareness of long-term consequences of repetitive head injuries, concussive or sub-concussive, have made it a popular topic in the media and research. The National Institutes of Health held a consensus meeting in 2016 with the aim of defining the neuropathological criteria for CTE diagnosis [126].

They blindly evaluated 25 cases of various tau proteinopathies, including CTE and a number of dementing brain diseases, and the results demonstrated reasonably good agreement and improved specificity to the diagnosis of CTE.

There is some controversy in the incidence rate of CTE and if the presence of tau protein represents trauma-induced CTE versus normal deposits as a result of age and other life factors [127]. Some researchers suggest a very high incidence of CTE in anyone who participated in a contact sport, with rates as high as 75–99% [124, 128]. All of these studies have been done by post-mortem analysis of brain tissue, which is currently the only way to definitely diagnose CTE [129]. However, several studies have been performed since 2017 which have brought uncertainty to the clinical manifestations and incidence of CTE, i.e., the patterns of behavior and cognitive deficits experienced by the living individual affected by CTE. Retired contact-sport athletes have be shown to have no differences in cognition [130, 131], mild cognitive impairment [132], executive function [133], or structural or functional brain differences [134]. This suggests that although Tau proteins may deposit in the brain after head-injuries, they do not causes significant decrease in function unless it is very severe.

11. Conclusion

PCS is a complex disorder and its pathophysiology is not clearly understood. There are no symptoms, or group of symptoms, that can accurately diagnose PCS. Females may be at a higher risk of developing PCS than male. Although there are no advanced imaging biomarkers for PCS, some studies present differences in those patients who predominantly complain of mood-related or cognitive symptoms when compared with other sub-types of PCS. Longitudinal changes in the brain have been identified in PCS up to 1 year since concussive head injury. ANS dysfunction is observed in PCS, which could be due to damage to the ANS control centers located in the hindbrain or uncoupling of the connections between the central ANS and cardiovascular system. Abnormal cardiovascular metrics suggest ANS dysfunction and impaired CBF regulation, which may explain the characteristic finding of symptom-limited exercise intolerance in physiological PCS. Functional imaging, like fMRI, has shown differences between healthy people and patients with PCS, but these differences are not consistent in the literature. Long term consequences of PCS or repetitive concussions include CTE, but the clinical manifestations of CTE need to be studied in greater detail. Therapies for PCS include sub-threshold aerobic exercise, which may increase neuroplasticity and decrease neuroinflammation through release of BDNF. More research needs to be done to identify objective biomarkers of concussion, PCS, and recovery, as well as therapies for PCS.

Acknowledgements

Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under award number 1R01NS094444. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest

The author does not declare any conflicts of interest.

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