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ORIGINAL ARTICLE

Physiological, vestibulo-ocular and cervicogenic post-concussion disorders: An evidence-based classification system with directions for treatment

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Abstract

Primary objective: To present a novel pathophysiological approach to acute concussion and post-concussion syndrome (PCS).
Research design: Review of the literature
Methods and procedures: PubMed searches were performed to identify articles related to the pathophysiology and treatment of concussion and PCS. Relevant articles that contributed to the primary objective of the paper were included.
Main outcome and results: This paper presents an evidence-based approach to acute concussion and PCS that focuses on the identification of specific post-concussion disorders (PCDs) caused by impairments in global brain metabolism (Physiologic PCD) or neurological sub-system dysfunction (Vestibulo-ocular PCD and Cervicogenic PCD) that can be distinguished by features of the clinical history, physical examination and treadmill exercise testing. This novel approach also allows for the initiation of evidence-based, multi-disciplinary therapeutic interventions that can improve individual symptoms and promote efficient neurological recovery.
Conclusion: Future studies incorporating neuro-imaging and exercise science techniques are underway at the author's institutions to validate this novel pathophysiological approach to acute concussion and PCS.

Keywords

Concussion, post-concussion syndrome, physiology, treatment

History

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Introduction

There is growing healthcare, government and media attention concerning concussion as an emerging public health issue among children, adolescents and adults. There are an estimated 1.6–3.8 million sport-related concussions annually in the US [1]. Although the vast majority of patients who sustain a concussion will reach full neurological recovery within 1–2 weeks, ~15–20% will demonstrate persistent signs and symptoms lasting greater than 3 weeks [2]. Risk factors for prolonged recovery include younger age, female gender, prior concussion history and history of learning disabilities or migraine headaches [3–6]. Patients that do not return to their pre-injury neurological baseline after the expected timeframe are at risk for further co-morbidities including aerobic de-conditioning, chronic pain, anxiety disorder, depression, as well as poor academic performance [7–9]. The management of athletes with sub-acute concussion and post-concussion syndrome (PCS) remains controversial and poorly established. Typically, because many of the signs and symptoms of PCS are non-specific, are similar to the patient's presenting complaints and seem to reflect global neurological dysfunction, patients are instructed to physically and cognitively rest until symptoms resolve spontaneously [10]. While such a conservative approach seems reasonable and is supported by expert opinion, it does not take into consideration the pathophysiological processes that underlie individual signs and symptoms.

This paper presents a unique approach to acute concussion and PCS that focuses on the identification of dysfunction within specific neurological sub-systems. Broadly speaking, it is proposed that the symptoms and impairments reported by patients in the post-concussion recovery period form symptom 'clusters' that point to operational post-concussion disorder (PCDs) that can be identified by salient features of patient history, physical examination and aerobic treadmill testing. Each PCD is characterized by persistent pathophysiological alterations in specific neurological sub-systems (in the case of cervicogenic PCD and vestibulo-ocular PCD) or global brain metabolism (in the case of physiologic PCD). Although considerable overlap between PCDs may exist in any individual patient, the presence of each PCD has important implications for patient prognosis and return-to-play (RTP) decision-making. More importantly, the ability

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to recognize and distinguish between these operational PCDs allows for the initiation of tailored, evidence-based therapeutic interventions that can improve individual disabling symptoms and promote efficient neurological recovery.

Initial assessment

Pathophysiology

Experience from experimental animal models of concussion and neuro-imaging studies in adults and children with traumatic brain injury (TBI) have begun to shed light on the pathophysiological mechanisms underlying concussion. Among the processes occurring on a molecular level are alterations in cell membrane permeability, ion transport regulation, neurotransmitter release, cellular metabolism and cerebral blood flow (CBF). To summarize briefly, the acute phase of concussion is characterized by the release of excitatory neurotransmitters resulting in widespread neuronal depolarization and dysregulation of ions including potassium and calcium [11]. To restore homeostasis, these ion imbalances are met with up-regulation of adenosine triphosphate (ATP)-dependent sodium-potassium pumps and subsequent increases in cellular glucose metabolism demands. Following this initial period of hypermetabolism, mitochondrial dysfunction leads to a protracted period of decreased glucose utilization and metabolism, the duration of which is unclear and during which the brain may be at increased vulnerability to repeat trauma [12]. In healthy individuals CBF is tightly coupled to cerebral metabolism, whereby an increase in neuronal activity and metabolism results in increases in regional and global CBF. However, in patients with TBI this coupling process is impaired and, instead of up-regulating cerebral perfusion to meet metabolic needs, cerebral hypoperfusion ensues leading to further secondary injury [13]. Although the magnitude and temporal pattern of these cerebrovascular alterations have an important predictive impact on patient outcomes in severe TBI [14], the role of these factors in paediatric and adult concussion remains unknown. Clinical and research experience suggest that, during this 'acute energy crisis', repeat brain trauma is detrimental and poorly tolerated, as evidenced by the rare but catastrophic 'second-impact syndrome' [15].

Clinical history

The recognition and diagnosis of concussion remains challenging due to the wide variability in clinical manifestations associated with this condition and a persistent poverty of knowledge among participating athletes, parents and even practicing physicians. Nonetheless, the initial signs and symptoms associated with acute concussion are largely reflective of global neurological dysfunction and the consequences of the aforementioned acute energy crisis. Common symptoms of acute concussion include headache, nausea, intermittent vomiting, disturbances of balance or gait, dizziness, tinnitus, photophobia, phonophobia, difficulty focusing, slowed speech, light-headedness or fogginess, extreme fatigue and impairments in cognitive processing and memory. Common signs of acute concussion include retrograde or anterograde amnesia, disorientation, confusion, gait imbalance and memory deficits [16]. Although the signs and symptoms are often easily recognized and extracted from an adult patient's history, children and adolescents very often do not have the insight or vocabulary to identify these features. It is recommended that paediatric physicians phrase interview questions in contexts that are appropriate to the childhood population. Inquiring about the child's experience in grocery stores, walking up stairs, playing video games and driving in the car will often illicit confirmatory evidence that those activities make the child feel anxious, foggy or 'not right'. The key distinguishing feature of acute concussion symptoms relate to the effect of physical and cognitive activity. In the setting of acute concussion, patients will often find that even low demand activities such as walking up stairs, reading, watching television, texting or phone conversations will exacerbate their symptoms.

Physical examination

The focus of the initial physical examination should not only be to assess the severity of the concussion and its effects on neurological sub-systems, but to also screen for findings indicative of more serious pathology such as occult intracranial haemorrhage or cervical spine instability. A full description of all the elements of a complete physical examination is beyond the scope of this review. At a minimum, the initial examination of patients with acute concussion should include a full neurological exam including testing of cranial nerve, motor, sensory, reflex and cerebellar function. The examination should also include a thorough assessment of balance, gait and cognitive functions such as speech and memory. Finally, a thorough assessment of the cervical spine should be performed and baseline heart rate (HR) and blood pressure measurements recorded.

In the vast majority of patients, a screening neurological examination will reveal no abnormalities [10]. Patients with prominent balance and dizziness complaints may demonstrate impairments on balance and gait testing, while those with a history of whiplash-type injuries may show tenderness and decreased range of motion of the cervical spine. Subtle findings in the oculomotor, vestibular and cervical spine examinations can be further investigated with the use of special or provocative testing (which will be covered in the following sections). Importantly, any focal neurological deficit such as weakness, numbness, slurred speech or visual impairment should alert the physician to consider serious intracranial pathology. Likewise, any severe neck pain, limitations in range of motion, alignment abnormalities or radicular symptoms should raise the suspicion of underlying cervical spine pathology [17].

Management

In the majority of patients, the time course associated with symptom resolution is highly correlated with the temporal profile of physiological recovery observed in experimental animal models of concussion and human neuro-imaging studies. Consequently, it is believed the symptoms of acute concussion are chiefly reflective of a global cerebral energy crisis and must be managed appropriately. Patients with acute concussion should be withheld from sporting activities and be

exposed to adequate periods of physical and cognitive rest for a 1–2-week period. At this stage, many patients will benefit from a clear treatment plan communicated to the patient, parents and teachers that permit significant school and work accommodations, thereby limiting cognitive demand to a level that minimizes symptom recurrence or exacerbation [18]. Once asymptomatic at rest, athletes should be permitted to engage in a graduated RTP protocol consisting of: light aerobic activity, sport-specific exercise, non-contact training drills, full-contact practice and return to play [10]. Patients may also benefit from graduated academic programmes or Return-to-Learn protocols that can help re-engage patients back to full academic participation [18]. Lastly, patients and parents must be educated on the signs and symptoms of concussion as well as the risks of repeated concussion. In the vast majority of uncomplicated concussions, patients are able to return to school, work and sporting activities without functional impairment.

Secondary assessment

Approximately 80–85% of patients with concussion will recover to their neurological baseline within 1–2 weeks. For the remaining 15–20% with persistent symptoms, guidelines for management have not been established. Historically, patients complaining of persistent symptoms such as headache, dizziness, imbalance, fogginess and difficulty concentrating have been lumped together as suffering from PCS, a unifying diagnosis with no available treatment. Working on the suspicion that the global physiological processes that underlie the initial brain injury have yet to resolve, this population has been instructed to continue with physical and cognitive rest in a sustained effort to minimize symptoms [10]. While such a conservative approach seems reasonable, it does not take into consideration the pathophysiological dysfunction of neurological sub-systems that mediate individual signs and symptoms.

Instead of viewing all patients with persistent symptoms 3-weeks post-injury as a uniform population of PCS, it is believed that unique features of the patient's clinical history, physical examination and results of graded treadmill exercise testing can point to distinct sub-types or post-concussion *disorders* (PCD) characterized by persistent pathophysiological alterations in specific neurological sub-systems or in global brain metabolism. Operationally, these sub-types are defined as: physiologic PCD, vestibulo-ocular PCD, and cervicogenic PCD. Although many patients may demonstrate symptoms reflective of more than one sub-type, it is believed that the following scheme is helpful in localizing persistent impairments to specific neurological sub-systems or higher-order cerebral dysfunction. Distinguishing between global and sub-system dysfunction is not only important from a prognostic perspective but allows for the initiation of targeted therapeutic strategies to help minimize symptoms and enhance recovery. The pathophysiology, clinical history, physical examination findings, graded treadmill testing results and treatment strategies for each PCD sub-type are presented in the following sections and summarized in Table I. Although it is believed that all patients of all age groups with concussion and PCD should be managed by healthcare providers with training and experience in concussion, it is in the unique population of children and adolescents with persistent symptoms that a comprehensive, evidence-based, patient-centred approach to this condition is most imperative.

Physiologic PCD

Physiologic PCD is characterized by persistent concussion symptoms and impairments caused by continued alterations in global cerebral metabolism.

Pathophysiology

It is hypothesized that the pathophysiological basis of Physiologic PCD is characterized by persistent alterations in cell membrane permeability, ion transport regulation, neurotransmitter release, cellular metabolism and cerebral blood flow that have yet to fully recover after the patient's initial injury. Although patients with Physiologic PCD may report mild persistent symptoms or be asymptomatic at rest, they continue to have exacerbation of symptoms during cognitive activity and/or physical exercise, reflective of a persistent cerebral metabolic energy deficiency. Evidence to support a physiological basis for this clinical pattern has begun to emerge. For example, Maugans et al. [19] demonstrated reductions in mean resting CBF using phase contrast MR-angiography in adolescents with sport-related concussion that persisted despite symptom cessation and neuropsychological test normalization. One of the mechanisms that may contribute to alterations in CBF and contribute to prolonged recovery following concussion is autonomic nervous system dysfunction. Patients with concussion and TBI have been found to have higher rates of sympathetic nervous system output than controls, as exemplified by higher resting heart rates [20] and higher heart rates during cognitive [21] and physical exercise [22]. The role of autonomic nervous system regulation in concussion recovery is not clear but may be mediated by effects on cerebrovascular reactivity. Importantly, exercise has emerged as a potential strategy to promote ANS and concussion recovery [23–25]. While exercise has been found to increase parasympathetic nervous system activity, decrease sympathetic nervous system activity [26] and increase CBF [27], the timing of employing exercise as a treatment for patients with concussion is pivotal. In animal experiments, Griesbach et al. [28, 29] found that premature exercise within the first week post-injury led to impaired cognitive performance and reduced levels of peptides important in mediating nervous system recovery and plasticity such as brain-derived neurotrophic factor. Alternatively, animals exposed to aerobic exercise 14–21 days post-injury were found to have improved cognitive performance and higher levels of neurotrophic peptides compared to those treated with rest. Taken together, these studies suggest that symptoms of Physiologic PCD are mediated by persistent alterations in cerebral cellular metabolism that can be managed successfully with controlled, individualized exercise treatment programmes.

Clinical history and physical examination

The clinical history and physical examination findings of patients with Physiologic PCD are similar to those observed

Table I. Summary of pathophysiology, predominant symptoms, pertinent physical examination findings, graded treadmill test results and treatment options in patients with PCDs.

	Physiologic PCD	Vestibulo-ocular PCD	Cerviogenic PCD
Pathophysiology	• Persistent alterations in neuronal depolarization, cell membrane permeability, mitochondrial function, cellular metabolism, and cerebral blood flow	• Dysfunction of the vestibular and oculomotor symptoms	• Muscle trauma and inflammation • Dysfunction of cervical spine proprioception
Predominant symptoms	• Headache exacerbated by physical and cognitive activity • Nausea, intermittant vomiting, photophobia, phonophobia, dizziness, fatigue, difficulty concentrating, slowed speech	• Dizziness, vertigo, nausea, lightheadedness, gait instability and postural instability at rest. • Blurred or double vision, difficulty tracking objects, motion sensitivity, photophobia, eye strain or brow-ache, and headache exacerbated by activities that worsen vestibulo-ocular symptoms (i.e. reading)	• Neck pain, stiffness, and decreased range of motion • Occipital headaches exacerbated by head movements and not physical or cognitive activity • Lightheadedness and postural imbalance
Physical exam findings	• No focal neurological findings • Elevated resting HR	• Impairments on standardized balance and gait testing • Impaired VOR, fixation, convergence, horizontal and vertical saccades	• Decreased cervical lordosis and range of motion • Paraspinal and sub-occipital muscle tenderness • Impaired head-neck position sense
Graded treadmill test	• Graded treadmill tests are often terminated early due to symptom onset or exacerbation	• Patients typically reach maximal exertion without exacerbation of vestibulo-ocular symptoms on graded treadmill tests	• Patients typically reach maximal exertion without exacerbation of cervicogenic symptoms on graded treadmill tests
Management options	• Physical and cognitive rest • School accommodations • Sub-symptom threshold aerobic exercise programs should be considered for adolescent and adult athletes	• Vestibular rehabilitation program • Vision therapy program • School accommodations • Sub-symptom threshold aerobic exercise programs should be considered for adolescent athletes	• Cervical spine manual therapy • Head-neck proprioception re-training • Balance and gaze stabilization exercises • Sub-symptom threshold aerobic exercise programs should be considered for adolescent and adult athletes

PCD, post-concussion disorder; VOR, vestibulo-ocular reflex.

during the initial assessment. At 3 weeks post-injury some patients may continue to endorse symptoms such as headache, nausea, intermittent vomiting, disturbances of balance or gait, dizziness, photophobia, phonophobia, difficulty focusing, fogginess and fatigue [9]. The characteristic headache observed in Physiologic PCD is similar to that described during the initial assessment and is often exacerbated by cognitive and physical activity, especially long days at school. Patients may report modest improvements in cognitive function and attention. Importantly, because their health status has limited sport and school participation, it is at this stage that children and adolescents begin to suffer changes in mood including sadness, irritability and depression, which may only come to light if parents are asked specifically about these changes.

Treadmill testing

In adult and adolescent patients with persistent symptoms 3 weeks post-injury, graded aerobic treadmill tests have emerged as a safe, reliable and effective tool to help quantify physiological recovery, distinguish between PCD sub-types and guide RTP decision-making [7, 30]. Using a standardized Balke protocol, patients perform an incremental treadmill exercise test to the point of symptom onset or exacerbation or until maximal exertion is achieved (defined as a rating of perceived exertion, RPE, of 18–20 on the Borg scale). During this test, heart rate and RPE are measured at 1-minute intervals. At maximal exertion or at the first sign of symptom onset or exacerbation, the test is terminated and total exercise time and heart rate at peak exertion are recorded and used to estimate oxygen consumption. Following the test, patients are monitored until their baseline symptom and cardiovascular status have been achieved. Using this technique, physicians can proceed through the algorithm outlined in Figure 1. Patients who are minimally symptomatic or asymptomatic at rest and who reach maximal exertion without symptom exacerbation are deemed to be ‘recovered’ and safe to return to aerobic activities including non-contact sports-related play (Step 3 of the Return-to-Play guidelines [10]). Patients with symptoms at rest 3 weeks post-injury who experience a symptom-limited threshold during the treadmill test are classified as having Physiologic PCD. Patients with symptoms at rest 3 weeks post-injury without a symptom-limited threshold on the treadmill test should undergo further physical examination to identify the source of their persistent symptoms; for example, are the symptoms attributable to isolated dysfunction of the vestibulo-ocular system (vestibulo-ocular PCD) or of the cervical spine somatosensory system (cervicogenic PCD)? It is important to emphasize that, although graded treadmill testing can be performed safely in patients with concussion, it should be performed only in

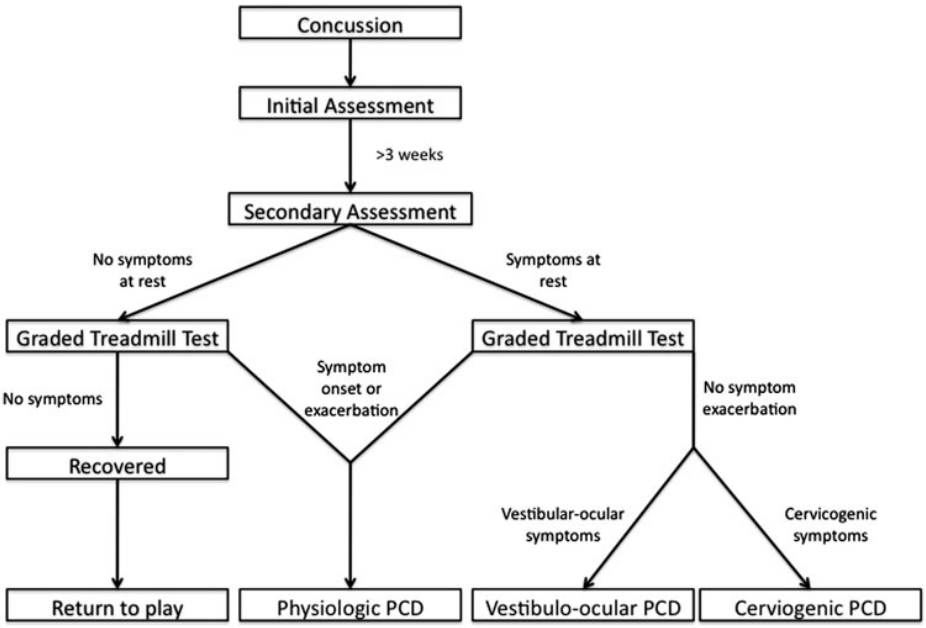

Figure 1. Proposed algorithm for diagnosis of PCD sub-types. PCD, post-concussion disorder.

patients at low cardiac risk for maximal exertion and under the supervision of a physician and experienced exercise specialists [31].

Management

The management of Physiologic PCD, especially in children and adolescents, is controversial, must be individualized and should only be carried out by physicians with significant experience managing paediatric concussion patients. Given that Physiologic PCD is mediated by persistent alterations in global cerebral cellular metabolism, expert guidelines suggest that any patient with persistent post-concussive symptoms should be managed with cognitive and physical rest without any other intervention [10]. For patients with significant symptoms at rest, this conservative approach is the safest and will result in complete neurological recovery in the majority. However, emerging evidence has begun to suggest that sub-symptom threshold exercise training may hasten recovery and improve functional outcomes in adolescents and adults with concussion. Leddy et al. [7] compared the outcomes of 12 PCD patients who were symptomatic at rest and who experienced symptom exacerbation during graded treadmill testing. All patients were prescribed aerobic exercise for the same duration they achieved during treadmill testing but at 80% of the maximum heart rate achieved, once daily, 5–6 days a week, with use of a digital heart rate monitor. Patients were instructed to have another person supervise them during exercise. Follow-up clinical assessments and treadmill tests were scheduled every 3 weeks until the patient could exercise to exhaustion without symptom exacerbation during treadmill testing. No adverse events occurred during the study. Following treatment, all reported reduced symptoms, treadmill times from baseline to treatment termination doubled and all patients achieved significantly greater peak heart rate and systolic blood pressure values without symptom exacerbation. Athletes recovered much faster than non-athletes. Importantly, the rate of symptom improvement was highly correlated with the exercise intensity achieved, suggesting that symptom improvement parallelled improvements in physiological recovery. In a later study the same group retrospectively compared the functional outcomes of 63 adolescents and adults with Physiologic PCD and non-physiologic PCD (i.e. those who could exercise to capacity). Overall, 72% of patients who complied with the exercise programme, including 77% of those with Physiologic PCD and 64% of those with non-physiologic PCD, returned to full daily functioning [23].

At this time, continued cognitive and physical rest is recommended for children with Physiologic PCD. Although adolescents will also benefit from continued cognitive and physical rest, individualized sub-symptom threshold aerobic exercise programmes should be considered in adolescent and adult athletes with symptoms that persist beyond 3 weeks, especially when managed by experienced physicians. As with acute concussion, children and adolescents will also continue to benefit from academic school accommodations and Return-to Learn programmes [18].

Vestibulo-ocular PCD

Vestibulo-ocular PCD is characterized by persistent concussion symptoms and impairments caused by dysfunction of the vestibulo-ocular system.

Pathophysiology

The integration of the vestibular, oculomotor and somatosensory systems is necessary to allow human beings to optimally navigate and function within a complex visuospatial environment. This complex system is comprised of highly specialized neural networks that interact at multiple levels of the craniospinal axis to regulate gait, maintain balance and

postural control, as well as co-ordinate eye movements. Specifically, this system consists of special sense organs (the retina, semi-circular canals and otolithic organs and joint mechanoreceptors) with primary processing units that share rich direct, indirect and reciprocal projections to the spinal cord, ANS, brainstem nuclei, cerebellum, thalamus, basal ganglia and cerebral cortex [32]. Components of these systems include the vestibulo-ocular reflex (VOR) which regulates gaze stabilization during head acceleration and the vestibulo-spinal reflex (VSR) which co-ordinates head, neck and trunk positioning during dynamic body movements. Dysfunction within components of these neurological sub-systems can have adverse effects on related sub-systems, thereby generating complex symptoms and impairments that are difficult to localize to one specific neural substrate. Symptoms of dizziness, gait instability, fogginess, blurred vision and difficulty focusing can arise from dysfunction at multiple levels of the vestibulo-ocular system, the exact pathophysiology of which remains poorly understood. In the setting of TBI, vestibular symptoms such as vertigo and dizziness have been found to arise from post-traumatic benign paroxysmal positional vertigo (BPPV), labyrinthine concussion, perilymphatic fistula, endolymphatic hydrops, otolith disorders and central vestibular disorders with more than one mechanism present in up to 46% of patients [33]. Common visual complaints such as blurred vision, diplopia, difficulty reading or motion sensitivity have been found to arise from subtle deficits in accommodation, version (pursuits, saccades and fixation), convergence insufficiency as well as photosensitivity and, rarely, visual field defects and cranial nerve palsies [34, 35]. Without an informed, organized, neuroanatomical approach to PCD, these symptoms and impairments can be easily attributed to metabolic PCS with the expectation that clinical improvement will only occur once the global cerebral energy crisis has resolved. Alternatively, if these features are recognized as dysfunction of the vestibulo-ocular sub-system, then tailored rehabilitation programmes can be initiated to treat specific symptoms and restore sub-system function.

Clinical history

Symptoms arising from dysfunction of the vestibulo-ocular system are amongst the most debilitating and disabling impairments associated with concussion. They are also among the most difficult complaints to ascertain from the patient history, especially in children and adolescents. It has been noticed that younger children often do not have the vocabulary or insight to describe the effects that vestibulo-ocular dysfunction has on subtle aspects of their perceptional processing. In order to identify the features of vestibulo-ocular PCD, the need to phrase questions in the context of the child's daily life cannot be over-stated. Common complaints that point to vestibular dysfunction include: dizziness, vertigo, nausea, light-headedness, gait instability and postural instability at rest. These complaints are often elicited by walking on unstable surfaces or abrupt changes in posture, head position or walking direction. Common complaints that point to related dysfunction in the oculomotor system include: intermittent blurred or double vision, difficulty tracking objects, motion sensitivity, photophobia, eye strain or brow-ache, trouble focusing and headache. In paediatric patients, vestibulo-ocular dysfunction is often most apparent in the setting of school or other visually stimulating environments. Upon questioning, children and adolescents will often report difficulty losing their spot or skipping words when reading, difficulty copying notes off the board at school, feeling 'outside of' or 'one step behind' themselves or describe feelings of intense anxiety or overwhelming nausea when they are in the halls at school during recess, are working on a computer for long periods, are driving in a car or accompanying their parents to the grocery store. While children may not be able to explain the exact features of the scenarios that precipitate their symptoms, these features undoubtedly point to perceptual difficulties related to navigation of complex visuospatial environments. Importantly, although patients with vestibulo-ocular PCD may endorse complaints of headache, they are often related to activities that exacerbate their vestibular and oculomotor complaints and are not typically exacerbated by aerobic physical activity.

Physical examination

In addition to the full neurological examination discussed in the *Initial Assessment* section, patients with vestibulo-ocular PCD should undergo careful examination of balance and gait as well as the vestibular and oculomotor systems. Apart from conventional tests such as the Romberg test and gait examination, standardized balance and gait examinations are useful in quantifying vestibular dysfunction. The Balance Error Scoring System (BESS) has been validated in children, adolescents and adults and has compared favourably to laboratory-based posturography such as the Sensory Organization Test in patients with concussion [36]. The Dynamic Gait Index (DGI) and Functional Gait Assessment (FGA) are scored instruments used to assess increasingly complex gait involving changes in speed, head turns and walking around obstacles. It is also important that patients with symptoms of BPPV be screened with the traditional and side-lying Dix-Hallpike tests that can identify candidates that may benefit from otolith repositioning manoeuvres.

Examination of the visual and oculomotor systems should start with a thorough examination of visual acuity, visual fields, pupillary function, fundoscopy and gross extra-ocular movements. Additional oculomotor examination techniques can help identify more subtle oculomotor deficits. Ocular alignment can be tested with cover–uncover tests that can help reveal esophorias, exophorias, hyperphorias and hypophorias. Examination of convergence and vergence can help quantify convergence insufficiency. Version should be assessed in the setting of horizontal, vertical and diagonal saccades and smooth pursuits. Symptoms of dizziness, blurred vision or headache precipitated by these manoeuvres are very common in patients with vestibulo-ocular PCD and their resolution is a good gauge of recovery of this sub-system. The final component of the vestibulo-ocular examination is testing of the VOR that can be performed in the horizontal or oblique planes and tested in both sitting and standing positions as well as while ambulating. Clinicians should document which examination techniques re-create or

exacerbate vestibulo-ocular symptoms, as this information is useful in devising rehabilitation programmes.

Treadmill testing

Patients with isolated vestibulo-ocular PCD are able to exercise to exhaustion during graded treadmill tests [31], suggesting that their persistent symptoms are caused by localized dysfunction of the vestibulo-ocular sub-system and not as a consequence of a persistent global cerebral metabolic deficit.

Management

An emerging body of evidence supports the use of vestibular therapy and repositioning techniques as effective treatments to improve dizziness and vertigo in patients with peripheral vestibular disorders [37, 38]. More recently, this effective treatment strategy has been shown to improve vestibular function in patients with TBI and concussion [33, 39, 40]. The underlying goal of vestibular rehabilitation is to recalibrate depth and spatial perception under static and dynamic conditions by re-establishing efficient integration of the vestibular, visual and somatosensory sub-systems. Current evidence suggests that vestibular rehabilitation programmes that utilize a 'top-down' approach and are customized to the patient's specific vestibulo-ocular deficits are the most successful [41]. Vestibular rehabilitation programmes should be designed to improve function of the VOR, the cervico-ocular reflex (COR), depth perception, somatosensory retraining, dynamic gait and aerobic conditioning [41]. Each of these areas can be addressed with home therapy programmes that utilize specific exercises that increase in difficulty according to the patient's impairments and progress. Increasing the velocity of these tasks, changing the base of support, changing directions and increasing the complexity of the visuospatial environment and lighting are important techniques to help expose the patient to more challenging conditions. For instance, patients with dizziness and vertigo with impairments in eye–head co-ordination can benefit from exercises that target the VOR. Alternatively, patients with postural imbalance and gait instability will benefit from exercises that modify their base of support and the stability of the walking surface [42]. Although the exact cause of vestibular dysfunction in patients with concussion may not always be evident, it is important to identify patients with central vestibular dysfunction and those with post-traumatic BPPV. Studies suggest that those with central vestibular dysfunction may be less responsive to vestibular re-training exercises [43], while those with BPPV have a high rate of responsiveness to otolith re-positioning manoeuvres [44].

Similar to vestibular rehabilitation therapy, increasing evidence also supports the use of vision therapy programmes in patients with TBI and concussion [34, 35, 45]. In one study of 160 patients with TBI, 90% were found to demonstrate improvement in oculomotor dysfunction after vision therapy [45]. Vision therapy programmes must be customized to address specific oculomotor deficits identified on the history and physical examination. Vision therapy programmes consist of exercises that aim to improve function in fixation, pursuit, predictable and unpredictable saccades, vergence and accommodation. Patients with significant impairments in reading can also benefit from specialized reading exercises [46].

Most importantly, vestibular and vision rehabilitation programmes should only be prescribed by licensed clinicians with significant experience in these disciplines and should only be targeted to specific neurological deficits identified on clinical history and physical examination. Because patients with vestibulo-ocular PCD do not manifest symptoms that are exacerbated by physical exertion, it is also recommended that these patients be prescribed aerobic exercise programmes that can help limit the physical de-conditioning that is often observed in this population.

Cervicogenic PCD

Cervicogenic PCD is characterized by persistent concussion symptoms and impairments caused by dysfunction of the cervical spine somatosensory system.

Pathophysiology

Clinical studies in patients with whiplash-type injuries and concussion and experimental studies with animals and humans have established the important role of the cervical spine in mediating balance, head orientation and eye movement. The high density and complexity of muscle and joint mechanoreceptors throughout the cervical spine are a rich source of proprioceptive information that is conveyed to multiple levels of the CNS, including the cerebellum, brainstem and spinal cord. Specifically, cervical afferents carry proprioceptive information to the cerebellum via the spinocerebellar tracts and to the dorsal column nuclei via the posterior column–medial lemniscal pathways, which project on to the thalamus and the primary somatosensory cortex. In addition, cervical afferents project to the central cervical nucleus, the vestibular nuclei and superior colliculi to mediate head and neck position sense through the co-ordination of several integrated reflexes, including the cervicocollic reflex (CCR), the vestibulocollic reflex (VCR) and the cervico-ocular reflex (COR) [47]. Dysfunction of these reflexes can lead to symptoms similar to those of vestibulo-ocular PCD including dizziness, gait instability, light-headedness, mental fogginess and visual disturbances. Both the CCR and the VSR work in a co-ordinated fashion to recruit the deep cervical muscles to help stabilize the head during head and body movements. The CCR is elicited by rotation of the body with the head fixed in place, leading to activation of the deep cervical muscles to help stabilize the head relative to the trunk [48]. The VCR is mediated by the vestibular system leading to activation of the deep neck muscles, which allows head stabilization in space during rapid head movements [49]. The COR is evoked by neck muscle stretch and combines with the VOR to co-ordinate head and eye movement during object tracking, contributing to gaze stabilization and re-orientation [50]. Mechanisms of cervical spine somatosensory dysfunction after whiplash-type injury and concussion are not clearly understood. Postulated mechanisms include alteration in mechanoreceptor functioning secondary to trauma or inflammation [47, 51, 52] and the central modulatory effect of pain and the sympathetic nervous system on cervical

somatosensory integration [53, 54]. Cervical afferent dysfunction may also be responsible for the pathogenesis of neck pain and headaches that accompany cervicogenic PCD. Musculoskeletal dysfunction within the upper cervical spine can lead to local pain as well as referred headache owing to the convergence of upper cervical spine nociceptive information within the trigeminocervical nucleus, which also receives general somatic sensory input from the face and head via the trigeminal nerve [55]. Significant differences in cervical muscle strength development, ligamentous laxity, head–body proportions and cervical spine mobility may place children and adolescents at increased risk of cervicogenic PCD and potentially concussion.

Clinical history

Patients with cervicogenic PCD often describe impact mechanisms that involve rapid acceleration–deceleration forces that are not only applied to the head but also the cervical spine. This may include incidents where they receive tackles or body checks that impact the craniocervical junction or in which they experience rapid hyperextension from a frontal head impact or hit the back of their head on the playing surface. The predominant complaints of patients with cervicogenic PCD consist of neck pain, stiffness, fatigue and decreased range of motion. Patients may also complain of associated symptoms such as dizziness and postural instability, but in children and adolescents these often manifest as light-headedness, nausea, fogginess or feelings of being 'detached' or 'out of it'. In many patients, these complaints are exacerbated by rapid head movements and may also be exacerbated by reading and school activities, particularly if they have poor posture during cognitive or physical activity. If present, headaches often originate from one or both occipital regions and can radiate forward into the temples and the eyes or into the cervical spine. Unlike physiologic PCD, these headaches are not typically exacerbated by aerobic physical exertion, but often get worse throughout the day.

Physical examination

In addition to the full neurological examination discussed in the *Initial Assessment* section, patients with cervicogenic PCD should undergo careful examination of the cervical spine, posture and gait. Patients that endorse significant vestibular and ocular symptoms should also undergo examination of those related neurological subsystems. Examination of the cervical spine should include assessment of overall cervical spine alignment and musculature. Cervical lordosis is often reduced in patients with cervicogenic PCD, with frequent static head tilts observed. Palpation of the cervical musculature may reveal diffuse muscle spasm and tenderness involving the paraspinal and suboccipital muscles as well as the anterior scalenes. Tenderness is often most prominent along the distribution of the greater and lesser occipital nerves, which may evoke the patient's described headache pattern. Range of motion of the cervical spine should be assessed in flexion, extension, lateral flexion and rotation. Attention should be paid to restricted movements and those that evoke associated vestibular symptoms. In order to assess the integrity of the cervical spine somatosensory system, patients should undergo assessment of cervical joint position error, which consists of assessing the patient's ability to relocate their head to a neutral position or perform smooth tracking manoeuvres while wearing a light-weight headband with a forward-facing penlight affixed to it. The patient's relocation error can be measured following flexion, extension and rotation and be used as an outcome measure for rehabilitation exercises [56].

Treadmill testing

Patients with cervicogenic PCD are capable of exercising to exhaustion during graded treadmill tests [31], suggesting that their persistent symptoms are caused by localized dysfunction of the cervical spine somatosensory system and not as a consequence of a persistent global cerebral metabolic deficit.

Management

The goal of a rehabilitation programme for cervicogenic PCD is to restore normal somatosensory output from cervical afferents and re-calibrate their connections to the vestibular and oculomotor sub-systems. Accordingly, these programmes should include exercises and techniques that improve neck pain and range of motion, strengthen and stabilize the cervical spine musculature and re-train the head and neck proprioceptive system. Techniques that can reduce pain and improve range of motion include stretching, passive and active range of motion exercises, massage and low velocity cervical spine mobilizations. Exercises that target the head and neck proprioceptive system include variations of the cervical joint position error exercises that can begin by having the patient relocate their head to neutral after extension and rotation with eyes closed and progress to relocation at varying points on the horizontal and vertical axis and then to tracing techniques such as figure of eights and other complex designs [47]. While many patients report improvements in neck pain, range of motion and headache following manual therapies, there is only modest empirical evidence to support their use in patients with cervicogenic headache [57] and whiplash [58], with no prospective studies investigating their use in concussion. However, some authors have observed significant improvements in neck pain, range of motion and disability in patients with whiplash when comprehensive programmes targeting cervical joint position re-training, balance, gaze stabilization and pain management are applied [47, 59, 60]. Finally, because patients with cervicogenic PCD often do not manifest symptoms that are exacerbated by aerobic physical exertion, it is also recommended that these patients be prescribed aerobic exercise programmes that can help limit the physical de-conditioning that is often observed in this population.

Post-traumatic mood disorders

Although the vast majority of PCD patients can be classified using the patho-physiological approach presented here, there remains a small but important proportion of patients who present with primarily affective symptoms including depression, anxiety and sleep disturbance. The management

of PCS patients with affective symptoms is challenging because of the extensive overlap between symptoms of PCS and mood disorders such as major depression and anxiety disorders [61]. Symptoms of major depression include depressed mood, loss of interest, fatigue, sleep disturbance and difficulty concentrating. Symptoms of anxiety disorders such as general anxiety disorder, post-traumatic stress disorder and acute stress disorder include feeling keyed up or on edge, fatigability, irritability, difficulty concentrating and difficulty falling or staying asleep. In the authors' experience, patients with PCS who present with primarily affective symptoms are capable of exercising to exhaustion during graded treadmill tests without symptom exacerbation. Although this suggests the absence of an ongoing global cerebral metabolic deficit, extensive literature supports the role of a regional neurotransmitter as well as cerebral metabolic and blood flow imbalances in the pathophysiology of mood disorders [62–64].

While the prevalence of mood disorders has not been extensively studied among patients with concussion, a diagnosis of major depression alone has been observed in up to 67–77% of patients with TBI [65]. Patients with TBI also remain at an elevated risk of substance abuse [66], unemployment [67] and family disruption [68], all of which can impact the patient's mood and overall well-being. Because the aetiology of post-traumatic mood disorders consists of a complex interaction of organic, psychological and social factors, management of PCS patients with affective symptoms is best conducted in close collaboration with a paediatric or adult psychiatrist or psychologist with significant experience in the TBI population. Management of patients with post-traumatic mood disorders often requires a multi-disciplinary approach utilizing pharmacological and cognitive behavioural therapies [69]. Most importantly, while pharmacological agents such as anti-depressants can help relieve affective symptoms related to mood disorders, they also have the potential to mask symptoms of concussion. Because successful management of PCS affective symptoms and mood disorders may require long-term pharmacological therapy, it is important for concussion healthcare providers and mental health providers to work together to optimize patient safety during RTP decision-making.

Finally, emerging evidence suggests that patients with TBI and perhaps concussion are at an elevated risk of suicidal ideation, suicide [70] and even homicide [71]. Although many patients with PCS are reluctant to discuss affective symptoms as well as thoughts of suicide or homicide, concussion physicians must always inquire about whether the patient feels at risk to themselves or others. If any risk exists, these patients should be immediately referred to psychiatric crisis centres for evaluation and management.

Migraine headache

A second factor that deserves special consideration and may act as a potential modifier to the pathophysiological approach presented here is a history of migraine headache. Migraine headaches are characterized by paroxysmal attacks of severe, throbbing, unilateral headaches associated with nausea, photophobia and phonophobia [72]. Although symptoms of classic migraine may be readily recognized in otherwise healthy patients, they may be difficult to distinguish from those that are characteristic of other PCDs in the setting of concussion. Few studies have examined the clinical behaviour of pre-existing migraine headache following concussion [73]. There is some evidence, however, of greater neurocognitive dysfunction in patients with post-concussion migraine headaches vs those with post-concussion non-migraine headaches or without headache [74] and others have observed that migraine patients seem to be at an increased risk of sustaining a concussion and of having more severe and prolonged post-concussion symptoms [5]. In the authors' experience, the effect of concussion on migraine is quite unpredictable, with improvement in migraine headaches in some patients and worsening in others. Importantly, the successful management of migraine headache requires an individually tailored approach consisting of pharmacologic and non-pharmacologic measures [75]. For this reason, it is recommended that all management decision-making in patients with a history of migraine headache be carried out under close collaboration with a paediatric or adult neurologist with significant experience in migraine.

Summary and conclusion

The true value of disease or condition classification systems resides in their ability to simplify diagnostic information, predict outcome and guide therapeutic decision-making. Although there have been numerous attempts to classify concussion in the past, none of these systems take into account the pathophysiology of concussion nor direct patients toward evidence-based treatment options. Because of the wide variability in concussion-related symptoms and observed recovery as well as the effect of ongoing brain maturation in children and adolescents, it is very unlikely that one single classification system will be devised to operationally define and direct care in all patients with concussion. Despite this, it is believed that the proposed pathophysiological approach provides a framework to examine concussion-related symptoms on the basis of global cerebral metabolic or neurological sub-system dysfunction. Although many patients will overlap or not fit neatly into each of these PCD sub-types, it is believed that this approach allows the identification of patients with specific neurological sub-system dysfunction that may potentially benefit from multi-disciplinary evidence-based treatment options.

It must be emphasized that the goal of this paper is to present a pathophysiological approach to acute concussion and PCS for concussion physicians and should not be viewed as a 'how-to' manual for all healthcare practitioners interested in concussion. In the authors' view, children and adolescents with concussion represent a unique but vulnerable population of TBI patients whose care must only be undertaken by physicians with training and experience in paediatric concussion and often in collaboration with a multi-disciplinary team of licensed healthcare professionals.

Directions for future research

Future prospective studies combining exercise science and neuro-imaging techniques are required to validate the

pathophysiological approach presented here and are currently underway at the authors' institutions. Further evidence is required to identify how and why patients with Physiologic PCD have limited exercise tolerance due to symptom exacerbation. It is hypothesized that patients with Physiologic PCD have difficulty with CBF regulation and that, during exercise, CBF increases to an intolerable level. It is further hypothesized that CBF dysregulation can be simulated using advanced imaging combined with acetazolamide, a drug that increases CBF. It is also hypothesized that sub-threshold aerobic exercise treatment improves CBF regulation and, therefore, is an effective treatment for Physiologic PCD. This research is made possible only by having a reproducible strategy for diagnosis.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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