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Pathophysiology and Mechanism of Concussion

Anthony Muchiri Wangui[1*], David Kaniaru[2], Mary Wambui[2]

[1]Department of Health Promotion and Sports Science, Masinde Muliro University of Science and Technology, Kakamega, Kenya
[2]Department of Health Professional Education, Masinde Muliro University of Science and Technology, Kakamega, Kenya

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***Corresponding author:** Anthony Muchiri Wangui

Abstract **Original Research Article**

Concussion has been identified as a major concern and a risk to athletes and sportsmen especially those involved in contact sports. During concussion the brain is exposed to intense acceleration, deceleration and rotational forces, resulting in the stretching and distortion of the neural structures. A systematic review was performed to summarize and appraise the evidence of literature on pathophysiology of concussion. The review was guided and based on CCOHTA'S guidelines. Primary studies that were either describing pathophysiology, mechanism, occurrence, biomechanics of concussion were included. With the *Population* inclusive of all Patients of all ages with a clinical definition of concussion. Published literature was identified through a cross-database search of relevant DIALOG databases. parallel searches were performed on AgeLine, CINAHL, PubMed, The Cochrane Library, and the Health Economic Evaluations Database. Searches were limited to literature published from January 1995 (1990 for PubMed) onward, with results fused up to May 31, 2019. Published literature was identified through a cross-database search of relevant DIALOG databases. parallel searches were performed on AgeLine, CINAHL, PubMed, The Cochrane Library, and the Health Economic Evaluations Database. Searches were limited to literature published from January 1995 (1990 for PubMed) onward, with results fused up to May 31, 2019. The pathophysiology of concussion was discussed in three major sunheadings of Cerebral Blood Flow, Ionic Flux and Glutamate Release, The Diffuse Axonal Injury (DAI) and Second Impact Syndrome In concussion. In summary concussion leads to These changes are activated by the mechanical insult itself and lead to ionic disturbance, EAA "neurotoxicity," initial mitochondrial dysfunction, ROS-mediated damage, energy metabolism depression, alteration of gene expression, and ultimately variation of NAA concentration, the "surrogate" marker of the dysfunctional neurons. Prospective longitudinal studies are needed to better under- stand the underlying biological mechanism of acute concussive injury as it relates to chronic neuropathology.

Keywords: Pathophysiology, Concussion, Mild Traumatic Brain Injury, Traumatic Brain Injury, Kenya, Neural structures.

INTRODUCTION

Concussion has been identified as a high priority health issue in rugby unions and contact sports [1-4] becoming a major and common issue in most contact sports, such as rugby it is categorized as one of the of the most troublesome injuries facing the sports medicine physicians [5-8]. Concussions are a frequent occurrence in athletic endeavors, its rate exceeding that occurring in the general population by 50-fold. Traumatic brain injury (TBI) related to sports affects an estimated 1.6 to 3.8 million people annually in the United States [9]. The biomechanics and pathophysiology of concussion are still not well understood and may lead to potential significant sequelae from single or more commonly multiple concussions [10]. It is categorized as the most common form of Traumatic brain injury (TBI) worldwide [11, 12] this has created a great interest on Head injuries particularly in all sports because of the potential for concussions and even severe traumatic brain injuries [13]. In other studies concussion has been described as ''invisible injury.'' This is also due to the fact that a concussed athlete who is experiencing symptoms of concussion may not outwardly look any different from uninjured peers which in most cases they are confused with players suffering anxiety which is a psychological effect [14, 15]. Understanding the pathophysiology of concussion can help guide management and treatment

focusing on the underlying mechanism behind the symptoms of concussion during the recovery period [16].

METHODS

A systematic review was performed to summarize and appraise the evidence of literature on pathophysiology of concussion. The review was guided and based on CCOHTA'S guidelines for authors [17].

Study Selection Criteria

Study type: Primary studies that were either describing pathophysiology, mechanism, occurrence, biomechanics of concussion was included.

Population: Patients of all ages with a clinical definition of concussion that may have been discussed in the studies were included in the review.

Literature Search Strategy

Published literature was identified through a cross-database search of relevant DIALOG databases. parallel searches were performed on AgeLine, CINAHL, PubMed, The Cochrane Library, and the Health Economic Evaluations Database. Searches were limited to literature published from January 1995 (1990 for PubMed) onward, with results fused up to May 31, 2019. Gray literature was obtained through searching specialized rehabilitation databases and Web sites of health technology assessment and related agencies. Clinical trial registries were also examined and Sports Registries.

Data Extraction

Two reviewers independently examined and selected the studies to be used in the review; any disagreement was resolved through consensus. One reviewer extracted relevant information from the selected studies using a standardized form adopted from the CCOHTA.

Data Synthesis

A qualitative approach summarizing the characteristics and results of the selected studies was used for data synthesis. The results of the studies were not pooled quantitatively. The level of evidence concerning the mechanisms of concussion was determined subjectively by weighing several factors: the number of studies, the consistency of trends, the "robustness" of results (including statistical significance and results of sensitivity analysis), and the methodological quality of studies. There was no formal assessment of methodological quality however, the limitations and transparency (in terms of fulfilling the data extraction form items) of each study were noted. More weight was given to the higher quality studies.

RESULTS

Search Results

The table below shows the studies that met the inclusion criteria on the concussion.

Author, year (country)	Title	Study design	Comments
Signoretti, S., Lazzarino, G., Tavazzi, B., & Vagnozzi, R. 2011 (Rome, Italy) [18]	Pathophysiology; mechanism of concussion	Literature Review N= 89 articles	Concussion and Neuromarkers and Biomarkers
Wilberger, J. 2014 (pennyslavia, USA) [19]	Concussion Mechanisms and Pathophysiology	Clinical Review N=87 Book chapter	pathophysiology and potential sequelae of concussion. cerebral blood flow (CBF) and metabolic demand during concussion
Rahman, Z., Zidan, A., Food, U. S., & Khan, M., 2013 (USA) [20]	The Potential Impact of Various Physiological Mechanisms on Outcomes In TBI, mTBI, Concussion And PPCS	Clinical Review N=187	physiology of the outcome of TBI or mTBI, Recognizing pathophysiology as it relates to past medical history, family history, genetics, multiple system involvement and systemic peripheral contributions to central nervous system (CNS).

McCrory, P., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M., & Cantu, R. 2009 (Zurich) [21]	Consensus Statement on Concussion in Sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008	A revision and update of the recommendations developed following the 1st (Vienna) and 2nd (Prague) International Symposia on Concussion in Sport	Validation of the SCAT2. Gender effects on injury risk, severity and outcome. Pediatric injury and management paradigms. Virtual reality tools in the assessment of injury. Rehabilitation strategies (e.g., exercise therapy).
Chermann, J. F., Klouche, S., Savigny, A., Lefevre, N., Herman, S., & Bohu, Y. 2014 (Paris, France) [22]	Return to rugby after brain concussion: A prospective study in 35 high level rugby players	Prospective study performed from Sept 2009 to June 2012	Validated the study protocol for the management of concussion
Choe, M. C. 2016 [16]	The Pathophysiology of Concussion	Clinical review N=137	pathogenesis of concussion neurocognitive deficits and mood disturbances limited to symptomatic
Choe, M. C., Babikian, T., Difiori, J., Hovda, D. A., & Giza, C. C. 2012 [23]	A pediatric perspective on concussion pathophysiology	Recent Findings on Clinical reviews N=88	longer recovery time for high-school athletes compared with adults (college, professional) after concussion. more severe cognitive deficits, and high-school males perform worse on balance & testing than college athlete's post-concussion
Dorrien, J. M. 2015 [24].	History of Concussion and Current Functional Movement Screen Scores in a Collegiate Recreational Population	n-55 collegiate Athletes	Previous research suggests that neurological function appears to be altered in those with a history of concussion
Daneshvar, D. H., & Nowinski, C. J. 2011 [25].	T h e Ep i d e m i o l o g y of Sport-Related concussion	Epidemiology rates among sports in USA 1988-2004 seasons. N=	Concussions and head injuries may never be completely eliminated from sports. **B**etter data comes with an improved understanding of the types of actions and activities that typically result in concussions.
Romeu-mejia, R., Giza, C. C., & Goldman, J. T. 2019 [26]	Concussion Pathophysiology and Injury Biomechanics	Clinical and Empirical Reviews N=128	model research, neuroimaging, and biomechanical impact kinematics post-impact neurobiochemical cascade that is well sup- ported by basic science literature
Willer, B., & Leddy, J. 2006 [27]	Management of Concussion and Post-Concussion Syndrome.	Clinical Reviews N=56	Early return to vigorous training leads to return of symptoms.
Giza, C., & Angeles, L. 2016 (USA) [28].	Pathophysiology of Sports-Related Concussion : An Update on Basic Science and Translational Research.	Systematic and Clinical review N=92	Role of genetic markers is not clear in the acute response to concussion Recent clinical data have raised concern about the long-term effects of prior concussion on cognitive and motor function
Allen, B. B. 2017,	Pathophysiology and	Clinical Reviews	Return to Play Protocol

(NY, USA) [29]	Diagnosis *of Concussion*	N-110	Return To School Protocol

Clinical definition of concussion

Concussion has attracted several definitions over decades but clinically and over 3 international consensus conferences it has be defined and redefined by a panel of experts to unanimously agree that concussion is complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces [21, 30, 31]. This briefly describes concussion as a rapid onset of short-lived impairment of neurologic functions resolving spontaneously [18]. It has been proposed that concussions be classified as a subset of mild TBI because most of these injuries appear to resolve without permanent consequences [21].

Concussion may be associated with symptoms that may be prolonged in a small percentage of cases, but this symptoms in acute cases reflect on a functional disturbance rather than a structural injury or physical injury, which usually is confirmed by the absence of abnormalities on standard neuroimaging studies [32]. Finally, concussion may or may not involve loss of consciousness as indicated by some study [33].

There are still some uncertainties regarding the compelling pathomechanisms that are triggered by the biomechanical forces on the head and the resulting insult and that unfold thereafter. This contributes to affecting several Cellular processes that may include ionic flux, neurotransmitter release, cerebral blood flow (CBF), metabolism, synaptic function, and axonal connectivity [23]. A better Clinical explanation tends to explain concussion as the mildest form of the spectrum continuum that is Diffuse Axonal Injury (DAI). Most of the described insights on the pathophysiology of concussion originated from animal data and were subsequently confirmed using invasive monitors in cases of severe human TBI [34] in recent days, the use of advanced neuroimaging has allowed demonstration, with noninvasive methods, of many components of the neurometabolic cascade after concussion [35].

Basic Science Pathophysiology

Cerebral Blood Flow

Studies suggest that after a concussion the cerebral vasoreactivity maintains a constant supply of oxygenated blood to the brain, by rapidly responding to shifts in arterial CO2 [16]. Reduced and Diminished cerebral glucose uptake has been reported after concussive injury in young adults, but the duration of this perturbation is unknown [36]. There has been a notable change in Cerebral activity after the occurrence of Concussion with Diffuse cerebral swelling being the most immediate even after a single mild TBI has been reported in pediatric patients [37], as well as in pedigrees with potential genetic vulnerability due to an ion channelopathy [38]. Another contributor to secondary neural injury/ damage is altered CBF, which can result in the presence of both excess and inadequate perfusion. TBI effects on CBF may occur through alterations in cerebral autoregulation, vasospasm, and/or regional perfusion disturbances [23]. Studies allude that Some patients suffering from a mild form of concussion may be extremely susceptible to the consequences of even minor changes in cerebral blood flow, as well as slight increases in intracranial pressure and apnea [39]. Acute brain injury induced an increase in glucose utilization, this has been shown in the presence of low CBF in a number of animal studies [40, 41], and in humans with severe head injuries [36]. After the initial period of increased glucose unitization, the injured brain transitions into a period of depressed metabolism that may lead to long-lasting and worsening energy crisis [42].

Ionic Flux and Glutamate Release

Many reviews have been done to explain the post-concussive neurometabolic cascade. After concussion, the Glutamate, an excitatory amino acid, is released immediately following injury, and glutamate receptors can become altered [28, 43]. Barkhoudarian *et al*., [44] in their review illustrated that during concussive injury, shearing forces damage the neuronal membrane producing an efflux of potassium into the extracellular space and initiating a widespread release of glutamate [45]. This in turn binds to N-methyl-D-aspartate (NMDA) and D-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) ionic channels instigating further depolarization and influx of calcium ions. Depolarization results in an extensive B spreading depression of neurons and ATP-dependent Na+/K+ pumps become activated, which require high levels of glucose metabolism. Post- injury, the Na+/K+ pump quickly diminishes intracellular energy stores and neurons are forced to use glycolysis. Concomitantly, oxidative metabolism is further disturbed due to mitochondrial dysfunction and an upsurge in lactate pro- duction which contributes to localized acidosis, cerebral edema, and an increase in membrane permeability [46] but the direct evidence of diffuse abnormal neuronal excitation/inhibition in acute concussion can be obtained by examining depolarization of nerve cells soon after traumatic brain injury [19]. However, long-term perturbations may occur, resulting in neuronal vulnerability to further insults and/or be responsible for post-concussive symptoms [46].

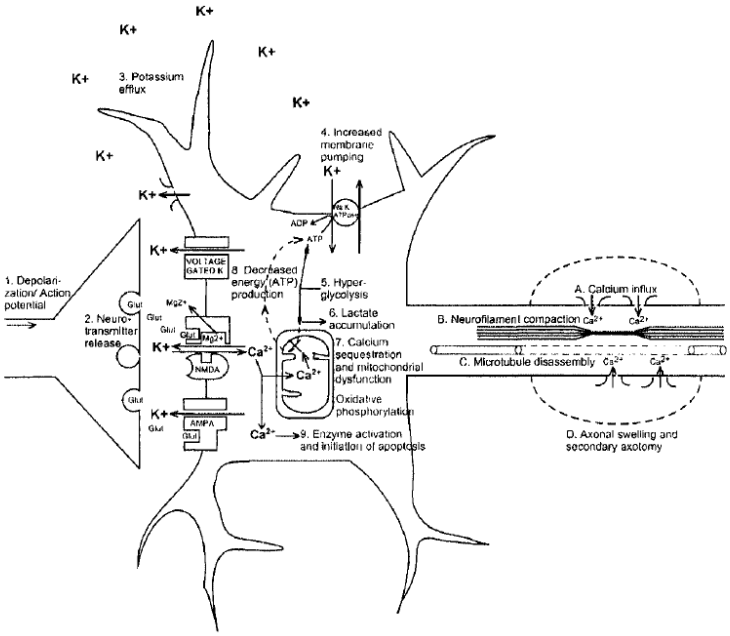

Fig-1: Neurometabolic cascade following traumatic brain injury. (1) Nonspecific depolarization and initiation of action potentials. (2). Release of excitatory neurotransmitters (EAAs). (3). Massive influx of potassium. (4) Increased activity of membrane ionic pumps to restore homeostasis. (5) Hyperglucolysis to generate more adenosine triphosphate (ATP). (6) Lactate accumulation. (7) Calcium influx and sequestration in mitochondria leading to impaired oxidative metabolism. (8). Decreased energy (ATP) production. (9) Calpain activation and initiation of apoptosis. A, Axolemmal disruption and calcium influx. B, Neurofilament compaction via phosphorylation or sidearm cleavage. C, Microtubule disassembly and accumulation of axonally transported organelles. D, Axonal swelling and eventual axotomy

The Diffuse Axonal Injury (DAI)

Diffuse axonal injury (DAI) is a common neuropathological finding after concussion causing diffuse, multifocal white matter lesions. It is a major contributor to morbidity after TBI [47-49]. A large body of clinical and experimental evidence suggests that such a distinctive course based on temporal neuronal dysfunction is an inevitable consequence of complex biochemical and neurochemical cascade mechanisms that are directly and immediately triggered by traumatic insult to the brain [50-54]. Diffuse axonal injury occurs regardless of the severity of the biomechanical effect. an injury results to an initial disruption of the axonal transport and an imminent swelling but more severe cases may result to Wallerian degeneration follows as a chronic and long-term process [55]. Axonal pathology is experienced in the initial 24h but can still be observed weeks to months later after the occurrence. The swelling is influenced by damage from the shear and tensile biomechanical forces as well as progressive changes on the cytoskeletal changes that impairs transport [49]. Periodic swellings and varicosities have been associated with partial microtubule breakage with undulations in axon morphology [56]. This axonal conduction deficits in unmyelinated fibers and if they persist in 2 weeks with preserved potential fiber action this contributes to a relative vulnerability of unmyelinated axons reflecting in a significant reduction in mean axonal caliber. These physical changes can reduce conduction velocity and may be correlated to cognitive and memory impairments seen after TBI [57, 58] consequently this affects the post injury symptoms and cognitive functions [59, 60] immune and autoimmune mechanisms, inflammatory pathways and oxidative phosphorylation or other energy production damage. Limits to the effectiveness of pharmaceutical and surgical approaches are apparent, and complicated by the physiological interconnectedness of such pathways [20].

Second Impact Syndrome in Concussion

Three athletes succumbed to death in 1984 after a minor concussion but all the three cases had an antecedent concussion from which they were still symptomatic- this characterizes the second impact syndrome as reported by Saunders & Harbaugh [61]. 50 such occurrences are reported [62, 63]. Several studies on sportsmen while still having symptoms from a previous head injury that unexpectedly and unpredictably led to sustained intracranial from a previous head injury, experienced a second injury that unexpectedly and unpredictably led to sustained intracranial hypertension and cata- strophic outcomes [61]. Further effects on the Cebrovascular are reported by Cantu and Voy [62] Ongoing cerebrovascular vulnerability at the time of the second concussion triggers massive vasodilatation and subsequent lethal brain swelling due to a marked increase in cerebral blood volume. This notion has been called into question by autopsy findings of acute subdural hematomas in 15-20% of cases [62]. This entity of the occurrence of catastrophic cerebral edema after mTBI/concussion is what is referred as second impact [64-67]. Several studies have potentially described the pathophysiology's of the second impact syndrome, Giza

& Hovda [68] describe the initial response to the impact is an acute abnormal glucose metabolism and energy crisis shortly after traumatic brain injury indicate a window for potential vulnerability in the traumatized brain [18] "A study of American high school and college football players demonstrated 94 catastrophic head injuries (significant intracranial bleeding or edema) over a 13-year period [69] Of these, only two occurred at the college level. Seventy-one percent of high school players suffering such injuries had a previous concussion in the same season, with 39% playing with residual symptoms" [70].

Summary

While our understanding of concussion pathophysiology has improved significantly in the past decade, the diagnosis remains an imperfect art. Large voids remain in our understanding of the pathophysiology and clinical presentation of concussion. In the absence of rapid and inexpensive diagnostic measures, it remains a clinical diagnosis that is subject to tremendous variability among clinicians. Sudden and profound biochemical changes occur after a concussive trauma. These changes are activated by the mechanical insult itself and lead to ionic disturbance, EAA "neurotoxicity," initial mitochondrial dysfunction, ROS-mediated damage, energy metabolism depression, alteration of gene expression, and ultimately variation of NAA concentration, the "surrogate" marker of the dysfunctional neurons. Understanding the basic pathophysiology of concussion as it occurs in the developing brain provides insight to link biological mechanisms with clinically relevant concepts such as duration of neurocognitive impairment, vulnerability to repeat injuries, perturbation of neuroplasticity and the potential for cumulative deficits.

Conflict of Interest

Anthony Muchiri, David Kaniaru and Mary Wambui each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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