

UCLA

UCLA Previously Published Works

Title

Concussion—Mild Traumatic Brain Injury Recoverable Injury with Potential for Serious Sequelae

Permalink

<https://escholarship.org/uc/item/46t4n6nd>

Journal

Neurosurgery Clinics of North America, 27(4)

ISSN

1042-3680

Authors

Kamins, Joshua
Giza, Christopher C

Publication Date

2016-10-01

DOI

10.1016/j.nec.2016.05.005

Peer reviewed



HHS Public Access

Author manuscript

Neurosurg Clin N Am. Author manuscript; available in PMC 2018 April 14.

Published in final edited form as:

Neurosurg Clin N Am. 2016 October ; 27(4): 441–452. doi:10.1016/j.nec.2016.05.005.

Concussion - Mild TBI: Recoverable Injury with Potential for Serious Sequelae

Joshua Kamins, MD [Resident Physician] and
Department of Neurology, University of California Los Angeles

Christopher C Giza, MD [Professor]
Departments of Pediatric Neurology and Neurosurgery, University of California Los Angeles

Synopsis

Concussion is increasingly recognized as a major public health issue. The majority of patients will return to baseline and experience full recovery, although a subset experience persistent symptoms. Newer animal models and imaging studies are beginning to demonstrate that metabolic and neurovascular resolution may actually take longer than symptomatic recovery. Repeat TBI within the metabolic window of dysfunction may result in worsened symptoms and prolonged recovery. The true risk for second impact syndrome appears to be small, and development of cerebral edema after a mild impact may be related to genetic risks rather than serial impacts. Additionally, there is mounting evidence that exposure to multiple concussions, despite an apparent return to normalcy, may increase risk for remote neurologic syndromes later in life. Subconcussive impacts have been described as head impacts that occur repeatedly and without neurological signs or symptoms, and have been proposed to contribute to delayed or progressive neurological deficits.

Keywords

Concussion; mild TBI; sequelae of concussion

I. Introduction

Although the original contemplation of concussion originated in Ancient Greece (Fig-1)¹, public and scientific awareness are finally gaining traction. The scientific establishment now recognizes that the consequences of mild Traumatic Brain Injury (TBI) might not always be so mild. With ongoing development of basic and clinical science, it becomes possible to

Corresponding Author Christopher Giza, Room 531 Wasserman, 300 Stein Plaza, Dept of Neurosurgery; Div of Pediatric Neurology, Mattel Children's Hospital - UCLA, Los Angeles, CA 90095 (cgiza@mednet.ucla.edu).
author Contact information

Joshua Kamins, UCLA Department of Neurology, 710 Westwood Plaza, Suite 1-240, Los Angeles, CA 90095-1769

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

disclosure statement

Disclose any relationship with a commercial company that has a direct financial interest in subject matter or materials discussed in article or with a company making a competing product. If nothing to disclose, please state "The Authors have nothing to disclose."

provide better prevention, assessment and treatment for concussions, particularly in higher risk groups like military personnel, athletes and pediatric patients.

II. Definitions

In order to proceed with a discussion of mild TBI and concussion, one must establish working definitions, as mild TBI and concussion are often used interchangeably. As seen in Table 1, mild TBI is historically based on Glasgow Coma Score (GCS), while concussion is a clinical syndrome that may overlap with mild, moderate, and severe TBI.

III. Epidemiology

Whether from increased awareness or an increased risk, the rate of reported TBI in the U.S. has been increasing. From 2001 to 2009, the number of annual TBI-related Emergency Department (ED) visits related to sports and recreation activities increased from 153,375 to 248,418, with the highest rates among males aged 10-19². However, the ED is just the tip of the iceberg, as it's estimated that there are greater than 700,000 mTBIs per year in high school athletes alone and over 13% of these are in patients with recurrent concussions³.

Sports related concussions have been on the rise, likely due to both increased recognition and increased power and strength in our athletes. In 2007, Hootman et. al.⁴ analyzed NCAA data from 1988 to 2004 regarding all injuries, including concussion. There was no significant change in overall rate of injury, however concussions did increase significantly over this interval. Surprisingly, women's soccer had the highest risk of concussion per 1000 athlete exposures with a rate of 0.41, which was not only higher than men's soccer at 0.28, but on par with men's football's risk of 0.37. This brought the idea to the forefront that women are not only at risk of concussion, but may be at a higher risk within the same activity compared to their male counterparts. Many theories have been proposed to explain this discrepancy including hormonal differences, weaker neck muscles, and higher rate of symptom reporting among female athletes. Multiple investigators have confirmed that among comparable sports, in which rules of play are similar, women have a higher rate of concussions^{5,6}.

IV. Pathophysiology

Concussion is a complicated syndrome of microstructural injury and functional impairment^{7,8}. The initial event after impact is dominated by a massive flux of ions and excitatory neurotransmitters, resulting in a metabolic crisis. Rat models show that after fluid percussion impact (FPI), ionic flux of sodium, potassium and calcium occurs, concomitant with a release of excitatory neurotransmitters, predominantly glutamate. Glutamate then generates further ionic imbalance transiently overwhelming the existing pumps on neurons and surrounding glial cells whose purpose is to maintain a precise transmembrane ionic gradient⁹. NMDA receptor activation then leads to further calcium influx.

The ionic pumps being activated are ATP driven, and to keep up with ATP depletion there is immediate hyperglycolysis. As TBI leads to decreased cerebral perfusion, this produces a neurovascular decoupling or metabolic mismatch, with high glucose demand and impaired

delivery. This is exacerbated by mitochondrial dysfunction caused by secondary effects of calcium influx. Moreover, magnesium is depleted, which persists for days following TBI. This is important because in addition to its roles in glycolysis, oxidative generation of ATP, and providing stability to cellular membrane potential, magnesium is an NMDA antagonist. Thus without magnesium, persistently open NMDA receptors lead to further calcium influx, intensifying the cycle described above.

In adult rats, the acute hypermetabolic state consisting of ion shifts, excitatory neurotransmitter activity and hyperglycosis is followed by a hypometabolic state lasting 7-10 days. During this subacute period, there is upregulation of cytokines and inflammatory genes along with microglial activation. In addition to this inflammation and the metabolic dysfunction, there is microstructural injury. Cytoskeletal damage can alter neurotransmission and at the severe end, result in axonal disconnection triggered by dismantling of the axonal cytoskeleton via caspases and calpain¹⁰.

While most of this neurometabolic cascade has been demonstrated in humans after severe TBI, there is a cerebrovascular effect demonstrable after both severe and mTBI. It has been proposed that concussion symptoms acutely and subacutely are related to this metabolic mismatch¹¹, which can be demonstrated in-vivo with depressed cerebral blood flow, both acutely and persisting up to 30 days post injury¹². Meier et al also demonstrated this depressed CBF at days 1 and 7 post injury with recovery in most subjects by 1 month. Those with persistent symptoms beyond 1 month were more likely to have persistently depressed CBF¹³.

V. Clinical Diagnosis of the Acute Concussion

In order to accurately diagnose concussion, one must learn its common signs and symptoms and determine which tools are accurate and validated for assisting in this clinical diagnosis.

Out of 544 high school sports concussions the most common acute symptoms were headache in 93.4%, dizziness/unsteadiness 74.6%, difficulty concentrating 56.6%, vision changes including sensitivity to light 37.5%, nausea 28.9%, drowsiness 26.5%, and amnesia 24.3%. Loss of consciousness was only present in 4.6% of their patients⁵. In college athletes, the average number of symptoms and symptom resolution time do not differ by sex. However, a larger proportion of concussions in male athletes included amnesia and disorientation, while female athletes were more likely to report headache, excess drowsiness, and nausea/vomiting¹⁴.

There is no sign, symptom, or clinical tool that is 100% sensitive or specific for diagnosing a concussion. It remains a largely clinical diagnosis and for this reason, the most important rule is “When in doubt, sit them out” to protect against the increased risk for a repeat concussion.

The provider should also be aware of available clinical tools to be used on the sideline or in clinic to aid in triage and diagnosis (Table 2). Tests are best used in combination. Most tests are intended for evaluation in a quieter location other than the sideline, although symptom

checklists, Maddock's questions and King-Devick have been used on the sideline or in locker room/clinics.

VI. Neuropsychological testing

A comprehensive examination of concussion patients would be incomplete without a thorough neuropsychological examination. The foundation of applying neuropsychological testing to concussed athletes began with Dr. Jeffrey Barth in the 1980s. In 2008, Broglio and Puetz published a meta-analysis of neuropsychological testing, and showed that along with postural tests and symptom reporting, neurocognitive functioning was significantly depressed acutely, and generally remained affected to a lesser degree for at least 14 days¹⁸.

Computerized cognitive testing (CCT) is becoming widespread in a sports setting, with no particular brand showing a clear superiority. The main advantages of CCT are administration to large groups of athletes simultaneously, automated randomization of tests (alternate forms), accurate measurements of response and reaction time, and straightforward scoring and data storage,¹⁹ while traditional pen and paper testing advantages are increased face time allowing customizable tests by the tester, the ability to judge fluency and verbal memory, the opportunity to take appropriate breaks and extensive normative data for many demographic groups. As with any assessment tool, clinical context and judgment must be used when interpreting CCT, which is best done in consultation with a neuropsychologist. Studies have shown decreased CCT scores associated with orthopedic injury or even urge to void, rather than concussion^{20,21}.

VII. Acute imaging

The majority of mTBIs have no CT imaging findings. The Canadian Head CT Rule was directed to solve this dilemma²². Out of 3,121 adults with mTBI, 8% of patients had a clinically important brain injury (any acute finding on CT requiring admission or neurological follow-up), 1% required neurosurgical intervention, and 4% were found with clinically unimportant lesions (mostly small SAH or contusions not needing intervention, determined insignificant with no intervention needed and doing well at 14 day follow-up). The investigators found five high risk features: failure to reach GCS of 15 within 2 hours of presentation, suspected open skull fracture, sign of basal skull fracture, vomiting >2 episodes, or age >65 years. Additionally, there were two medium-risk factors: retrograde amnesia >30 min and dangerous injury mechanism. Any single high risk factor was 100% sensitive for the patient needing neurosurgical intervention and Medium risk factors were 98.4% sensitive for a clinically important brain injury. In combination, the rule was found to be 92% sensitive for any injury on CT, including "clinically unimportant" lesions.

The New Orleans Criteria necessitates imaging for any patients with age>60, vomiting, headache, intoxication, persistent anterograde amnesia, evidence of trauma above clavicle, or a seizure on presentation²³. When compared to the New Orleans Criteria, the Canadian CT rule was found to have greater specificity for clinically important head trauma leading to less imaging and lower costs.

The Pediatric Emergency Care Applied Research Network (PECARN) resolved to differentiate low risk pediatric mTBIs from those with clinically significant injury. This algorithm rules imaging out for patients with normal mental status, no loss of consciousness, no vomiting, a non-severe injury mechanism, no signs of basilar skull fracture, and no severe headache. The negative predictive value was 99.5% with zero missed neurosurgical interventions²⁴. Externally validated in 2014, the authors found that “none of the children with a clinically important TBI were classified as very low risk by the PECARN TBI prediction rules”²⁵.

Acute MRI, while promising in several research studies comparing a cohort with clinical concussion to a control cohort, does not yet provide additional diagnostic or prognostic power in the evaluation of an individual patient. A study compared 75 mTBI patients to a control group with sprained ankles. CT and MRI were performed on all subjects, and MR included not only FLAIR, T2, SWI, and DWI, but also Diffusion Tensor Imaging. No significant differences were found between the two groups. Moreover, no differences were found in patients who turned out to have prolonged symptoms at 1 month, with the authors suggesting there was no prognostic value of acute MRI with DTI²⁶.

Conversely, the TRACK-TBI study enrolled 135 patients with mTBI who presented to a level I trauma center²⁷. All patients enrolled received a CT scan and an “early MRI” (at 12+/-3.9 days). Thirty seven (27%) had abnormal head CT (31 intracranial, 6 isolated skull fractures). Of the 98 patients with negative head CTs, 28% had abnormal MRIs (23 hemorrhagic axonal injury, 3 contusions, 4 extra axial hematomas). Outside of socioeconomic and CT findings, the strongest predictor of poor outcome was MRI presence of one or more brain contusions or the presence of diffuse axonal injury.

VIII. Repeat injury

The first step in management is always to remove the patient from any scenario where they risk further injury to decrease risk of a second concussion, which has been associated with greater symptoms and prolonged recovery. In a prospective cohort study with 2905 NCAA football players, 184 had concussions, 12 had a 2nd concussion in the same season and 11 of 12 repeat concussions occurred within 10 days of the first injury^{28,29}.

Moreover, following concussive brain injury in an animal model, there is a window of metabolic vulnerability.³⁰⁻³² A single mTBI resulted in significantly decreased cerebral metabolic rate of glucose (CMRglc), which returned to those of sham injuries by day 3. When a 2nd mTBI was introduced within 24h of the first, CMRglc was further depressed, and recovery was prolonged. However, if the two impacts were introduced 120h apart, the CMRglc values recovered as if they were single impacts. Additionally, the 24h rTBI rats had memory deficits beyond day 3, unlike the single mTBI or 120h rTBI animals. This study demonstrated increased physiologic risk during the metabolic window of vulnerability, with normal recovery if injuries were further apart.

In humans, Magnetic Resonance Spectroscopy (MRS) was used to examine effects of concussion on brain metabolism. Concussed athletes had significantly depressed metabolite

ratios of NAA to creatinine or choline, lowest at day 3 and recovering to baseline by day 30. Athletes all reported symptom freedom between days 3 and 15 despite persistent metabolic changes on MRS. In a separate study, patients who had a second concussive injury before the 15-day mark did not recover NAA peaks until 45 days post injury. This data mirrors that of Prins et al in that the compounded injury produced a more severe metabolic depression than the first, and required longer to recover.

IX. Second Impact Syndrome

Second impact syndrome (SIS) remains a controversial subject. It was first reported in 1984 by Saunders and Harbaugh, who described massive, fatal, cerebral edema after a second mTBI before recovery from a first TBI³³. In this initial case report, a 19 year old football player who allegedly suffered a concussion from a fight, returned to play 4 days later and suffered additional mTBI. This resulted in massive cerebral edema and death.

McCrorry argues that SIS is over-reported, based on a recall bias of the first TBI, and that it shows a clear geographic bias, given no reports of this syndrome outside of the United States³⁴. If SIS were a risk in the general population, youth boxers should be at particular risk from this syndrome. Massive cerebral swelling after mTBI does occur rarely but may not always require repeated impacts. Multiple case reports have recounted disproportionate cerebral edema to a single mild head injury in patients with a personal or family history of hemiplegic migraine related to a familial or de novo mutation in one of the CACNA1A calcium channel subunit genes³⁵⁻³⁷. Based on current understanding of concussion pathophysiology, other types of ion channel dysfunction are plausible contributing mechanisms.

X. Recovering from injury: balancing rest and exercise

Regardless of the risk of SIS, the mainstay method for management of acute symptoms is cognitive and physical rest, given that symptoms are worsened when the metabolic mismatch is challenged. This should be followed by gradual return to activity and lead to structured exercise to improve recovery.

In an effort to answer the question of how much to rest their athletes, Majerske retrospectively assigned 95 adolescent student athletes with concussion to 1 of 5 groups based on post injury activity levels³⁸. All of the athletes' neurocognitive scores and symptom scores improved over time, but there was a significant relationship between those with the highest and lowest levels of activity and lower neurocognitive scores, particularly visual memory and reaction time. Those with moderate activity were associated with the best symptom scores and neurocognitive performance. Similarly in a prospective cohort study, Brown et al concluded that those with the highest quartile of cognitive activity post injury had the longest duration of symptoms, while the subjects in the three lower quartiles all showed similar recovery rates³⁹. In a different study, patients with persistent symptoms showed benefit from a period of cognitive and physical rest, even months after concussion, although this study lacked a control group⁴⁰.

In 2015, Thomas et al compared the result of five days of strict rest post injury vs “usual care” in which the patients had 1-2 days of rest and then returned in a stepwise manner⁴¹. Patients in the strict rest group took significantly longer to recover compared to the usual care group. Additionally, the strict rest subjects had a higher overall PCSS score and total number of symptoms in the 10 day follow-up, suggesting that possibility that strict rest may change symptom reporting patterns, too.

In summary, data demonstrates that it is likely beneficial for the patient to have some amount of cognitive and physical rest and then transition back to full amount of activity.

It is well known that exercise has a beneficial role in a wide variety of psychiatric and neurologic diseases, varying from improving patient's negative response to stress, preserving cognitive function in aging and dementia⁴², recovering some of the observed depletion of important neurotransmitters in clinical major depression and anxiety, and functioning in a neuroprotective role in multiple sclerosis⁴³⁻⁴⁵. In the realm of concussion and TBI, there is uncertainty regarding how to advise our patients regarding exercise, given the fact that activity too early seems to hamper recovery, but the chronic symptoms may all benefit from exercise.

Preclinical studies showed that acute exercise after adult rat fluid percussion worsened performance on cognitive tasks. Given the fact that exercise normally upregulates brain growth factors (BDNF) and enhances expression of downstream plasticity markers, this was surprising. Interestingly, exercise within the first week after FPI appeared to interrupt the production of these intracellular signaling proteins, likely disrupting plasticity. In a follow-up study, delayed voluntary exercise was helpful in mitigating post-TBI spatial memory deficits. Moreover, when investigators used a BDNF inhibitor, this was found to block the effect of exercise^{46,47}. In a small clinical study, human subjects with refractory and persistent post concussive symptoms have been successfully and safely treated with 3 weeks of sub-maximal exercise⁴⁸.

Current data suggests that, although very early cognitive and physical activity may delay recuperation and increase symptoms, exercise and activity can be beneficial for brain recovery and plasticity following concussion. Prolonged rest can have detrimental effects, as evidenced from other conditions such as low back pain⁴⁹. It is important to avoid social isolation, worsening of the stress response, and depression and anxiety that can occur with prolonged restriction of normal activities, particularly in athletes.

XI. Cognitive restructuring

Cognitive restructuring is a therapeutic concept dating back to Bruner and Gage in the 1960's in which the patient is guided to challenge their own thoughts and misconceptions that can interfere with recovery. In primary care, this is akin to the concept of anticipatory guidance, namely, providing the patient and family with information and expectations of what is likely to happen (used commonly for families with newborns going home, during normal development in kids, and after vaccination). The goal with concussion is to facilitate recovery by teaching the patient to expect their symptoms will resolve.

As early as 1972, Relander et al published a series in BMJ in which post-concussion symptoms were ameliorated by a combination of physiotherapy and daily meetings with a physician who emphasized a good prognosis. In 1996, Mittenberg contrasted two groups evaluated in the Emergency Department for mTBI⁵⁰. The control group received standard ED care, whereas the intervention group underwent a brief cognitive restructuring intervention. They reviewed the nature and incidence of expected symptoms, were taught techniques for reducing symptoms, and were given instructions for gradual resumption of activities. The patients in the intervention group reported significantly shorter average symptom duration and significantly fewer symptoms at follow-up. Furthermore, it has been shown both in children and adults that an intervention as simple as providing an information booklet at 1 week post injury that outlines common symptoms associated with mild head injury, their likely time course, and suggested coping strategies, results in improved outcome^{51,52}.

XII. Post Concussion Syndrome

Despite the best efforts of clinicians, a significant minority of patients may develop chronic postconcussive symptoms, and receive a diagnosis of postconcussion syndrome (PCS)⁵³. This is defined by ICD-10 as organic and psychogenic disturbances observed after closed head injuries, including subjective physical complaints (i.e. headache, dizziness), cognitive, emotional, and behavioral changes. Estimates of PCS incidence range widely from 10% to 40% of patients⁵⁴. However, symptoms that would lead to a diagnosis of PCS⁵⁵ are not always specific and even a portion of orthopedic injury control subjects report moderate chronic symptoms. Additionally, patients underreport premorbid symptoms that overlap with PCS. This suggests a role for maladaptive thoughts and misattribution of symptoms, and an even larger role for prevention of PCS with anticipatory guidance.

According to the AAN Guidelines, a history of prior concussion demonstrates the strongest evidence for more severe/longer duration of symptoms and cognitive deficits, while younger age, early posttraumatic headache, fatigue/fogginess, early amnesia, alteration in mental status, or disorientation demonstrated probable evidence for prolonged recovery⁵⁶. Premorbid predictors of PCS also include personal or family history of migraine, mood disorders, or other psychiatric illness⁵⁷.

Given that post traumatic headaches are often the most refractory symptom, it is vital to recognize any patterns whether it be a new primary headache syndrome or medication overuse headache (which contributes to up to 70% of chronic post traumatic headaches). Post traumatic tension type or migraine headaches should be managed similarly to nontraumatic headache syndromes with appropriate use of prophylactic and abortive agents.

Management of mood disorders, most commonly depression and anxiety⁵⁸, is best done with a combination of continued cognitive restructuring, thorough evaluations by neuropsychologists, and consideration of referral for medical treatment by a psychiatrist.

As demonstrated above, exercise and cognitive therapy may play a large role in ameliorating persistent symptoms. Earlier this year, Gagnon organized a case series of 10 adolescents

who were slow to recover from sport related concussion, with symptoms lasting over 4 weeks⁵⁹. The patients were provided with a structured exercise program, visualization and imagery techniques, and education for the patient and family. Significant and clinically relevant decrease in symptoms at 6 week follow-up was observed. Replicating these results in larger cohorts is important and may have strong implications for concussion rehabilitation.

XIII. Potential for Long Term Sequelae

In addition to better identification and early management of concussion, there is growing concern of both the general public and the scientific community for the potential long term consequences of repeated impacts and concussions. Professional athletes are reporting neurocognitive problems, culminating in class action lawsuits filed by former players in both football and hockey. Included in the nearly \$1 billion settlement with the NFL are monetary awards for diagnoses of ALS, Alzheimer's disease, Parkinson's Disease, Dementia, and a postmortem diagnosis of Chronic Traumatic Encephalopathy (CTE). Of note, there is no requirement to prove that the players' injuries were caused by playing football to receive compensation from the settlement.

It is important to distinguish between the multiple possible consequences of repeated brain impacts, as not every symptom or problem reported following concussion or contact sports exposure is a harbinger of a degenerative condition. A differential diagnosis for chronic neurocognitive problems in this scenario would include post-concussion syndrome, chronic headache disorders, chronic neurocognitive impairment, hormonal deficits, anxiety, depression, exacerbation of premorbid conditions and neurodegenerative disorders (Parkinsons, Alzheimers, ALS, CTE).

Mechanistically, persistent alterations of white matter signal are reported using DTI suggesting axonal damage contributes to chronic problems. In a pediatric cohort, these changes are seen early after injury while the subjects were symptomatic, but persist at 4 months post-injury, even after most symptoms resolve⁶⁰. Moreover, "subconcussive injury" due to soccer heading has been associated with white matter microstructural and cognitive abnormalities in adults⁶¹. Other evidence of network dysfunction after remote sports concussion has been reported using detailed neuropsychological testing, event related potential (ERP) testing, motor examination, and transcranial magnetic stimulation (TMS). Nineteen healthy former athletes who had sustained 1-5 concussions during their career, but all >30 years prior, demonstrated subtle neuropsychological deficits in visual memory and executive function as well as corresponding differences on ERP. Moreover, they demonstrated decreased velocity of rapid alternating movements as well as altered activation patterns on TMS⁶².

In addition, preclinical studies suggest subacute and chronic endocrine impairment after TBI. Comparing a sham single injury to four repeat injuries with 24h intervals, investigators found that rTBI rats demonstrated a significant depression of circulating IGF-1 acutely and reduced levels of GH and IGF-1 at 1 month post injury³¹. Studies of human patients show

endocrinopathies or pituitary damage after more severe TBI, with only a few case reports following concussive injury.

It is important to note that not all longitudinal studies have shown neurologic consequences from exposure to sports at risk of concussion. Investigators identified all male students who played high school football between 1946 and 1956 in their county. They found no significant difference in dementia, Parkinson's or ALS among the 438 football players compared to their non-football playing counterparts. This absence of consequence for high school football likely demonstrates both a dose response to mTBI and a difference between amateur and professional athletes.

Many cognitive complaints are affected by anxiety, depression, and PTSD. Recognition and treatment of any underlying psychiatric disease must be an important component of a comprehensive cognitive evaluation for remote effects of concussion⁶³.

There has been mixed evidence with regards to risk for Parkinson's Disease. Overall, a history of TBI does seem to increase risk for PD, however additional studies have shown no increase from mTBI. This may suggest that the hazard originates from moderate to severe TBIs^{64,65}.

With regards to chronic or remote neurocognitive consequences, there are distinctions described between Chronic Neurocognitive Impairment (CNI), which is diagnosed clinically in living patients, and Chronic Traumatic Encephalopathy (CTE), currently a post-mortem pathologic diagnosis.

Although multiple cohort studies describe a consistent pattern of neurocognitive impairment in athletes with exposure to contact and collision sports, due to an absence of longitudinal data leading to pathology, the causal link between clinical and pathologic findings is yet to be fully established. The predominant theory is the presence of a unique neurodegenerative disorder, CTE, as opposed to the idea that multiple TBIs lead to diminished cerebral reserve and thus earlier clinical expression of age-related neurodegenerative diseases.

Proponents of the diminished cerebral reserve theory point to evidence that a history of moderate-severe TBI or stroke earlier in life may result in earlier expression of neurodegenerative diseases and that athletes often report lower force required with each subsequent concussion. This would predict an earlier expression of conventional age-related neurodegenerative diseases in patients with a history of head trauma compared to non-head trauma controls⁶⁶. Surveys of 513 retired NFL players implied cognitive impairment in 35.1%. A comparison of neurocognitive profiles in a subsample of this group to a clinical sample of patients with a diagnosis of MCI due to AD revealed a highly similar profile of impairments. The authors contend this supports lowered cerebral reserve over a distinct diagnosis of CTE.

The science behind CTE has been advanced greatly in the last two decades by Drs Omalu and McKee, each with their own scores for CTE type and staging⁶⁷. Dr. McKee defines CTE clinically by symptoms of irritability, impulsivity, aggression, depression, short-term memory loss and heightened suicidality that usually begin 8–10 years after experiencing

repetitive mTBI. Pathologically, there is atrophy of the cerebral cortex, thinning of the corpus callosum, ventriculomegaly, cavum vergae and fenestrated septum pellucidum. The 2015 NINDS/NIBIB consensus meeting gathered 25 blinded neuropathologists to attempt to differentiate a variety of pathologies from CTE. The panel defined the pathognomonic lesion of CTE as an accumulation of abnormal hyperphosphorylated tau (p-tau) in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci and in an irregular pattern⁶⁸. Supporters propose this is a distinctive pattern that results from forces due to TBI, and detractors argue that these patterns overlap greatly with other known pathologies^{69,70}. As mentioned, CTE currently remains a pathologic diagnosis, although efforts are underway to better characterize the clinical semiology associated with this syndrome. Recent advances in PET imaging, while not yet validated, show some promise to diagnose CTE in-vivo, leading to earlier detection and better clinical characterization of the disease⁷¹.

CONCLUSION

The moniker ‘mild TBI’ was originally based upon comparison using the GCS, which included severely injured patients rendered comatose by a traumatic injury. However, it is increasingly apparent that a subset of individuals with mTBI may develop persistent problems or, very rarely a catastrophic outcome. It is critical to recognize that not every acute symptom is necessarily due to concussion pathophysiology, as many conditions may mimic concussion and are part of the differential diagnosis (migraine, ADHD, anxiety, cervicogenic headaches, as well as rare but devastating cerebral edema with or without intracranial hemorrhage). Likewise, there is an extensive differential diagnosis for chronic symptoms after mTBI/concussion, including chronic headaches, exacerbation of pre-morbid conditions, anxiety, depression, misattribution of symptoms, PCS, CNI, CTE and other neurodegenerative conditions. Careful consideration of all possibilities, with a focus on treatable conditions and symptomatic intervention, as well as cognitive restructuring and education, should be the mainstay for providing optimal clinical care for those experiencing concussion.

ACKNOWLEDGEMENTS

The authors would like to thank Doug Polster PhD. and Talin Babikian PhD for their assistance with the neuropsychology literature.

For full transparency, all funding sources are listed. Grants/Research Support: NIH, NCAA, DoD, NFL-GE, Today's and Tomorrow's Children Fund, UCLA BIRC, UCLA FGP, UCLA Steve Tisch BrainSPORT program; Consultant: NFLNCP, NHLPA, Neural Analytics; Advisory Panel: LoveYourBrain, MLS, NBA, NCAA, Neural Analytics, USSF; Medicolegal: One or two cases annually; Speaker's Bureau: Medical Education Speakers Network; Stock Shareholder: None; Other Financial or Material Support: None; Other: Commissioner California State Athletic Commission (end 2/2015)

REFERENCES

1. McCrory PR, Berkovic SF. Concussion: the history of clinical and pathophysiological concepts and misconceptions. *Neurology*. 2001; 57:2283–2289. [PubMed: 11756611]
2. Gilchrist J, Thomas KE, Xu L, McGuire LC, Coronado V. Nonfatal TBI related to sports and recreation activities among persons aged 19 years. *MMWR*. 2011; 60(39):1337–1342. [PubMed: 21976115]

3. Castile L, Collins CL, McIlvain NM, Comstock RD. The epidemiology of new versus recurrent sports concussions among high school athletes, 2005-2010. *Br J Sports Med.* 2012; 46:603–610. [PubMed: 22144000]
4. Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: Summary and recommendations for injury prevention initiatives. *J Athl Train.* 2007; 42(2):311–319. [PubMed: 17710181]
5. Marar M, McIlvain NM, Fields SK, Comstock RD. Epidemiology of Concussions Among US High School Athletes. *Am J Sports Med.* 2012; 40(4):747–755. [PubMed: 22287642]
6. Lincoln AE, Caswell SV, Almquist JL, Dunn RE, Norris JB, Hinton RY. Trends in Concussion Incidence in High School Sports: A Prospective 11-Year Study. *Am J Sports Med.* 2011; 39(5):958–963. [PubMed: 21278427]
7. Giza CC, Hovda D a. The Neurometabolic Cascade of Concussion. *J Athl Train.* 2001; 36(3):228–235. [PubMed: 12937489]
8. Giza CC, Hovda DA. New metabolic cascade. *Neurosurgery.* 2014; 75
9. Katayama Y, Becker DP, Tamura T, Hovda D a. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg.* 1990; 73(6): 889–900. [PubMed: 1977896]
10. Büki A, Povlishock JT. All roads lead to disconnection? – Traumatic axonal injury revisited. *Acta Neurochir (Wien).* 2006; 148(2):181–194. [PubMed: 16362181]
11. Tan C, Meehan W III, Iverson G, Taylor J. Cerebrovascular regulation, exercise, and mild traumatic brain injury. *Am Acad Neurol.* 2014:1665–1672.
12. Maugans TA, Farley C, Altaye M, Leach J, Cecil KM. Pediatric Sports-Related Concussion Produces Cerebral Blood Flow Alterations. *Pediatrics.* 2012; 129(1):28–37. [PubMed: 22129537]
13. Meier TB, Bellgowan PSF, Singh R, Kuplicki R, Polanski DW, Mayer AR. Recovery of Cerebral Blood Flow Following Sports-Related Concussion. *JAMA Neurol.* 2015; 87106(5):530–538.
14. Wasserman EB, Kerr ZY, Zuckerman SL, Covassin T. Epidemiology of Sports-Related Concussions in National Collegiate Athletic Association Athletes From 2009–2010 to 2013–2014: Symptom Prevalence, Symptom Resolution Time, and Return-to-Play Time. *Am J Sports Med.* 2015
15. Guskiewicz KM, Ross SE, Marshall SW. Postural Stability and Neuropsychological Deficits After Concussion in Collegiate Athletes. *J Athl Train.* 2001; 36(3):263–273. [PubMed: 12937495]
16. Galetta KM, Barrett J, Allen M, et al. The King-Devick test as a determinant of head trauma and concussion in boxers and MMA fighters. *Neurology.* 2011; 76(17):1456–1462. [PubMed: 21288984]
17. Eckner JT, Lipps DB, Kim H, Richardson JK, Ashton-Miller JA. Can a Clinical Test of Reaction Time Predict a Functional Head-Protective Response? *Med Sci Sport Exerc.* 2011; 43(3):382–387.
18. Broglio SP, Puetz TW. The effect of sport concussion on neurocognitive function, self-report symptoms and postural control : a meta-analysis. *Sports Med.* 2008; 38(1):53–67. [PubMed: 18081367]
19. Iverson GL, Schatz P. Advanced topics in neuropsychological assessment following sport-related concussion. *Brain Inj.* 2015; 29(2):263–275. [PubMed: 25313596]
20. Hutchison M, Comper P, Mainwaring L, Richards D. The Influence of Musculoskeletal Injury on Cognition: Implications for Concussion Research. *Am J Sports Med.* 2011; 39(11):2331–2337. [PubMed: 21768531]
21. Lewis M, et al. The Effect of Acute Increase in Urge to Void on Cognitive Function in Healthy adults. *Neurorol Urodyn.* 2011; 30:183–187. [PubMed: 21058363]
22. Stiell IG, Wells G a. Vandemheen K, et al. The Canadian CT Head Rule for patients with minor head injury. *Lancet.* 2001; 357(9266):1391–1396. [PubMed: 11356436]
23. Kavalci C, Aksel G, Salt O, et al. Comparison of the Canadian CT head rule and the new orleans criteria in patients with minor head injury. *World J Emerg Surg.* 2014; 9(1):31. [PubMed: 24742359]
24. Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. *Lancet.* 2009; 374(9696):1160–1170. [PubMed: 19758692]

25. Schonfeld D, Bressan S, Da Dalt L, Henien MN, Winnett J a, Nigrovic LE. Pediatric Emergency Care Applied Research Network head injury clinical prediction rules are reliable in practice. *Arch Dis Child*. 2014; 99(5):427–431. [PubMed: 24431418]
26. Iivesmäki T, Luoto TM, Hakulinen U, et al. Acute mild traumatic brain injury is not associated with white matter change on diffusion tensor imaging. *Brain*. 2014; 137(7):1876–1882. doi: 10.1093/brain/awu095. [PubMed: 24818956]
27. Yuh E, Mukherjee P, Lingsma HF, et al. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. *Ann Neurol*. 2013; 73(2):224–235. [PubMed: 23224915]
28. Guskiewicz KM, Mccrea M, Marshall SW, et al. The NCAA Concussion Study. *J Am Med Assoc*. 2003; 290(19):2549–2555.
29. Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: evaluation and management of concussion in sports. *Neurology*. 2013; 80(24):2250–2257. [PubMed: 23508730]
30. Prins ML, Alexander D, Giza CC, Hovda DA. Repeated Mild Traumatic Brain Injury: Mechanisms of Cerebral Vulnerability. *J Neurotrauma*. 2013; 30(1):30–38. [PubMed: 23025820]
31. Greco T, Hovda D, Prins M. The effects of repeat traumatic brain injury on the pituitary in adolescent rats. *J Neurotrauma*. 2013; 30(23):1983–1990. [PubMed: 23862570]
32. Prins ML, Hales A, Reger M, Giza CC, Hovda D a. Repeat traumatic brain injury in the juvenile rat is associated with increased axonal injury and cognitive impairments. *Dev Neurosci*. 2011; 32(5-6):510–518.
33. Bey T, Ostick B. Second impact syndrome. *West J Emerg Med*. 2009; 10(1):6–10. [PubMed: 19561758]
34. McCrory P. Does second impact syndrome exist? *Clin J Sport Med*. 2001; 11(3):144–149. [PubMed: 11495318]
35. Kors EE, Terwindt GM, Vermeulen FLMG, et al. Delayed cerebral edema and fatal coma after minor head trauma: Role of the CACNA1A calcium channel subunit gene and relationship with familial hemiplegic migraine. *Ann Neurol*. 2001; 49(March):753–760. [PubMed: 11409427]
36. Malpas TJ, Riant F, Tournier-Lasserre E, Vahedi K, Neville BG. Sporadic hemiplegic migraine and delayed cerebral oedema after minor head trauma: a novel de novo CACNA1A gene mutation. *Dev Med Child Neurol*. 2010; 52(1):103–104. [PubMed: 19811514]
37. Curtain RP, Smith RL, Ovcacic M, Griffiths LR. Minor Head Trauma – Induced Sporadic Hemiplegic Migraine Coma. *Pediatr Neurol*. 2006:329–332. [PubMed: 16638514]
38. Majerske CW, Mihalik JP, Ren D, et al. Concussion in sports: Postconcussive activity levels, symptoms, and neurocognitive performance. *J Athl Train*. 2008; 43(3):265–274. [PubMed: 18523563]
39. Brown NJ, Mannix RC, O'Brien MJ, Gostine D, Collins MW, Meehan WP. Effect of Cognitive Activity Level on Duration of Post-Concussion Symptoms. *Pediatrics*. 2014; 133(2):e299–e304. [PubMed: 24394679]
40. Moser RS, Glatts C, Schatz P. Efficacy of immediate and delayed cognitive and physical rest for treatment of sports-related concussion. *J Pediatr*. 2012; 161(5):922–926. [PubMed: 22622050]
41. Thomas DG, Apps JN, Hoffmann RG, McCrea M, Hammeke T. Benefits of Strict Rest After Acute Concussion: A Randomized Controlled Trial. *Pediatrics*. 2015; 135(2):213–223. [PubMed: 25560444]
42. Groot C, Hooghiemstra AM, Raijmakers PGHM, et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing Res Rev*. 2016; 25:13–23. doi:10.1016/j.arr.2015.11.005. [PubMed: 26607411]
43. Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress. *Clin Psychol Rev*. 2001; 21(1):33–61. [PubMed: 11148895]
44. Giesser BS. Exercise in the management of persons with multiple sclerosis. *Ther Adv Neurol Disord*. 2015; 8(3):123–130. [PubMed: 25941539]
45. Clark PJ, Amat J, McConnell SO, et al. Running Reduces Uncontrollable Stress-Evoked Serotonin and Potentiates Stress-Evoked Dopamine Concentrations in the Rat Dorsal Striatum. *PLoS One*. 2015; 10(11):e0141898. [PubMed: 26555633]

46. Griesbach GS, Gomez-Pinilla F, Hovda DA. The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. *Brain Res.* 2004; 1016(2):154–162. [PubMed: 15246851]
47. Griesbach GS, Hovda DA, Gomez-Pinilla F. Exercise-induced improvement in cognitive performance after traumatic brain injury in rats is dependent on BDNF activation. *Brain Res.* 2009; 1288:105–115. [PubMed: 19555673]
48. Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clin J Sport Med.* 2010; 20(1):21–27. [PubMed: 20051730]
49. Malmivaara, a, Aro, T. The treatment of acute low back pain--bed rest, exercise therapy or ordinary activity? *Duodecim.* 1995; 111(22):2101–2102. [PubMed: 9841169]
50. Mittenberg W, Tremont G, Zielinski RE, Fichera S, Rayls KR. Cognitive-behavioral prevention of postconcussion syndrome. *Arch Clin Neuropsychol.* 1996; 11(2):139–145. [PubMed: 14588914]
51. P J, W C, R A, et al. Impact of early intervention on outcome following mild head injury in adults. *J Neurol Neurosurg Psychiatry.* 2002; 73(3):330–332. [PubMed: 12185174]
52. P J, W C, R A, et al. Impact of early intervention on outcome after mild traumatic brain injury in children. *Pediatrics.* 2001; 108(6):1297–1303. [PubMed: 11731651]
53. Mittenberg W, Strauman S. Diagnosis of mild head injury and the postconcussion syndrome. *J Head Trauma Rehabil.* 2000; 15(2):783–791. [PubMed: 10739967]
54. Mittenberg W, Canyock EM, Condit D, Patton C. Treatment of Post-Concussion Syndrome Following Mild Head Injury. *J Clin Exp Neuropsychol.* 2001; 23(6):829–836. [PubMed: 11910547]
55. Dean PJA, O'Neill D, Sterr A. Post-concussion syndrome: Prevalence after mild traumatic brain injury in comparison with a sample without head injury. *Brain Inj.* 2012; 26(1):14–26. [PubMed: 22107176]
56. Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: evaluation and management of concussion in sports. *Neurology.* 2013; 80:2250–2257. [PubMed: 23508730]
57. Morgan CD, Zuckerman SL, Lee YM, et al. Predictors of postconcussion syndrome after sports-related concussion in young athletes: a matched case-control study. *J Neurosurg Pediatr.* 2015; 15(June):589–598. [PubMed: 25745949]
58. Fann JR, Katon WJ, Uomoto JM, Esselman PC. Psychiatric disorders and functional disability in outpatients with traumatic brain injuries. *Am J Psychiatry.* 1995; 152:1493–1499. [PubMed: 7573589]
59. Gagnon I, Grilli L, Friedman D, Iverson GL. A pilot study of active rehabilitation for adolescents who are slow to recover from sport-related concussion. *Scand J Med Sci Sports.* Apr.2015
60. Mayer AR, Ling JM, Yang Z, Pena A, Yeo RA, Klimaj S. Diffusion Abnormalities in Pediatric Mild Traumatic Brain Injury. *J Neurosci.* 2012; 32(50):17961–17969. [PubMed: 23238712]
61. Lipton M, Kim N, Zimmerman M, et al. Soccer heading is associated with white matter microstructural and cognitive abnormalities. *Radiology.* 2013; 268(3):850–857. [PubMed: 23757503]
62. De Beaumont L, Theoret H, Mongeon D, et al. Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain.* 2009; 132(3):695–708. [PubMed: 19176544]
63. Ellis MJ, Ritchie LJ, Koltek M, et al. Psychiatric outcomes after pediatric sports-related concussion. 2015:5–8.
64. Gardner RC, Burke JF, Nettiksimmons J, Goldman S, Tanner CM, Yaffe K. Traumatic brain injury in later life increases risk for Parkinson disease. *Ann Neurol.* 2015; 77(6):987–995. [PubMed: 25726936]
65. Marras C, Hincapié CA, Kristman VL, et al. Systematic Review of the Risk of Parkinson's Disease After Mild Traumatic Brain Injury: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil.* 2014; 95(3):S238–S244. [PubMed: 24581909]
66. Randolph C, Karantzoulis S, Guskiewicz K. Prevalence and characterization of mild cognitive impairment in retired national football league players. *J Int Neuropsychol Soc.* 2013; 19:873–880. [PubMed: 23902607]

67. Jordan BD. The clinical spectrum of sport-related traumatic brain injury. *Nat Rev Neurol*. 2013; 9(4):222–230. [PubMed: 23478462]
68. McKee AC, Cairns NJ, Dickson DW, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol*. 2015
69. McKee AC, Stein TD, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. 2013; 136(1):43–64. [PubMed: 23208308]
70. Iverson GL, Gardner AJ, McCrory P, Zafonte R, Castellani RJ. A critical review of chronic traumatic encephalopathy. *Neurosci Biobehav Rev*. 2015; 56:276–293. [PubMed: 26183075]
71. Barrio JR, Small GW, Wong K, et al. In vivo characterization of CTE using [F-18]FDDNP PET brain imaging. *PNAS*. 2015; 112(22):E2981–E2981. [PubMed: 25964344]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Key Points

- Concussion is a clinical syndrome induced by biomechanical force causing neurological symptoms that recover in the majority of individuals.
- A minority of patients with concussion go on to develop persistent symptoms which may be disabling.
- Proper management of concussion includes protecting the individual from repeated injury, assessment for risk factors or comorbidities that may prolong recovery, symptomatic care, reassurance, initial rest and providing a planned gradual return to cognitive and physical demand.
- Remote deficits from mild TBI include motor, cognitive, and endocrine dysfunction and potential neurodegeneration, for which the mechanisms are still being elucidated.

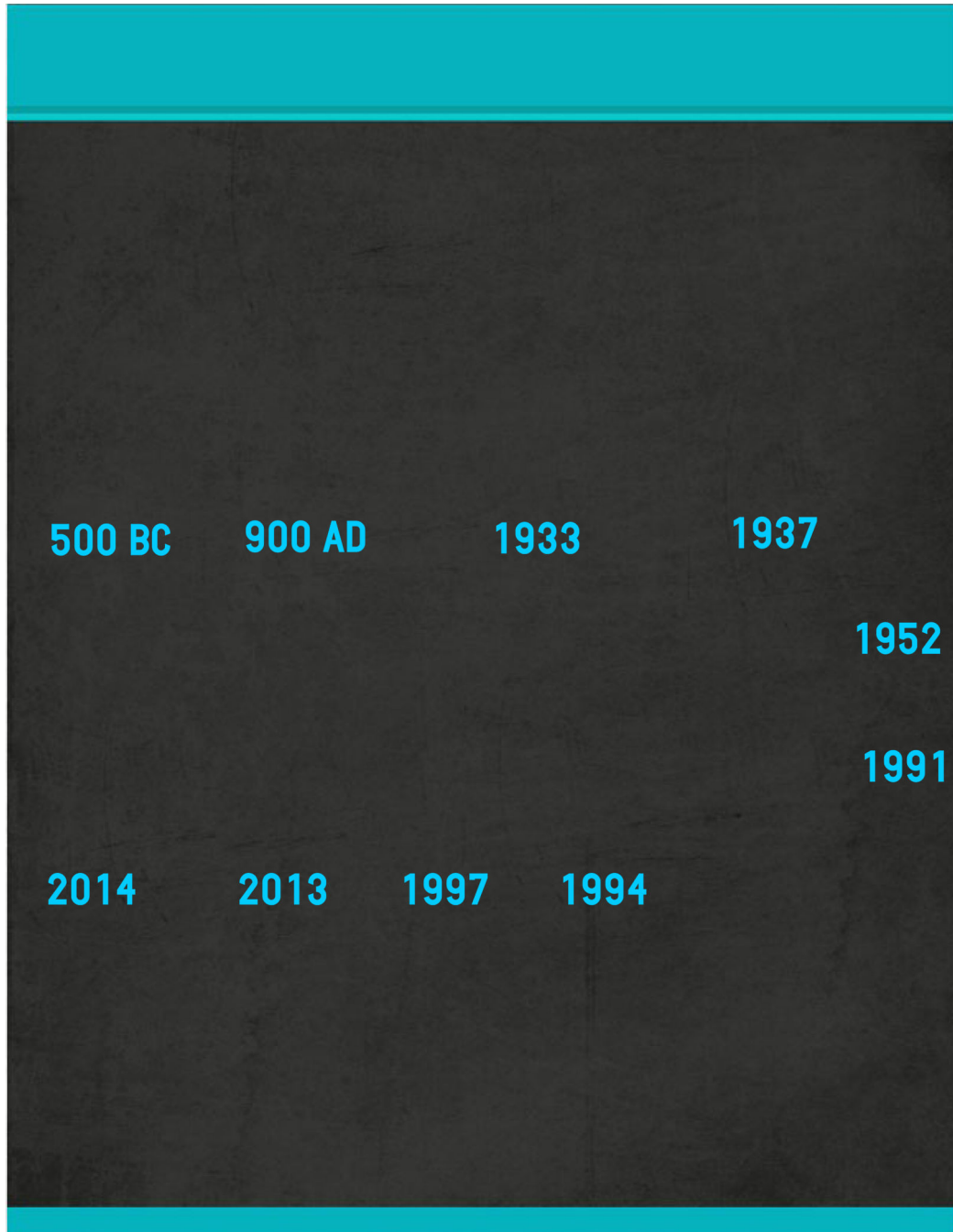


FIGURE 1.
History of Concussions

Table 1

TBI and Concussion Definitions

	Definition
Mild TBI (mTBI)	Traumatic brain injury, GCS of 13 to 15 within 24 hours of impact
Complicated mTBI	mTBI combined with intracranial imaging findings.
Concussion	Clinical syndrome in which a biomechanical force, via acceleration-deceleration or rotational forces, transiently disturbs normal brain function causing neurological-cognitive-behavioral signs and symptoms
Subconcussion	Proposed construct of biomechanical force causing subclinical injury in the absence of overt acute signs and symptoms.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Clinical tools for diagnosis

Test	Components	Pros	Cons
Standardized assessment of Concussion (SAC)	Orientation, immediate memory, concentration, and delayed recall	94% sensitivity and 76% specificity ¹⁰	Requires trained practitioner
Sports Concussion Assessment Tool (SCAT)	Symptom checklist, cognitive assessment (SAC), balance examination (BESS), and coordination examination	Validated, thorough examination combining multiple systems	Requires trained practitioner
Maddocks Questions	Orientation and recent memory related to ongoing sporting event	Brief, easy to administer, and ideal for sideline	Low sensitivity in isolation
Balance Error Scoring System (BESS) ¹⁵	Measurement of errors while balancing in 3 stances, both on firm ground and a foam pad	Practical test of vestibular networks, which are commonly affected in TBI	Poor inter-rater reliability
King-Devick ¹⁶	Indicator of saccadic performance	Sensitive test and easy to administer	Practice effect
Dropstick test ¹⁷	Measures clinical reaction time	Correlates with sport related reactions	Requires extra hardware

Data from Refs 10, 15-17.

Table 3

Characteristics of CNI and CTE

Chronic neurocognitive Impairment (CNI)	Chronic traumatic Encephalopathy (CTE)
Decrement in function	Neurodegenerative disease
May be static	Presumed progressive
Detected in living patients	Detected Post-mortem
May be measured by neuropsych testing or behavioral screening questionnaires	Characterized pathologically by tau accumulation
Causal link not yet established, but possible dose-dependent risk	Causal link not yet established, current data in case reports/series

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript