BASIC PATHOPHYSIOLOGY

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I. Introduction

Traumatic brain injury (TBI) in general has the highest incidence rates in infancy, adolescence-young adulthood and senescence. There is a 2-3:1 male:female predominance in the rates for TBI. Seventy-five to 80 percent of TBI is considered mild, many of which would qualify as concussions. It is estimated that 1.6-3.8 million sports-related brain injuries occur annually in the U.S.1 Among sports-related concussions, about 70-75% occur in boys. Interestingly, however, when sports with comparable rules between genders are compared (like soccer and basketball) the rates of concussion in girls outnumber boys 2:1 2. It has been suggested that this increased rate may be due to greater reporting of post-concussive symptoms in females; however, biological factors have also been implicated, such as weaker neck musculature or hormonal differences.

II. Neurometabolic Cascade of Concussion:

a. Acute symptoms and Time course

Concussion and TBI are known to be mediated through a complex neurometabolic cascade that was originally described in animal models and then also measured in humans with severe TBI 3,4. In concussion or mild TBI, it is believed that these events are recoverable with time, but a repeat injury can tip the physiological balance towards more permanent damage.

A spreading depression-like state of ionic flux may predispose to migrainous phenomena (headaches, photophobia, phonophobia) and potential for secondary injury. Clinical impairments in attention, memory, processing speed and reaction time may be driven by underlying impairments in neurotransmission or axonal dysfunction resulting in impaired network connectivity.

Experimental models of TBI have given substantial insight to perturbations of cerebral metabolism and function after concussive brain injury. In the rodent, following fluid percussion injury (FPI), there are measurable alterations in cerebral glucose metabolism, reductions in energy metabolites and evidence of mitochondrial dysfunction in the acute and subacute phases after injury. These abnormalities have been correlated with cognitive/behavioral deficits, which generally recover on a parallel time course 5,6. Furthermore, these physiological and behavioral disturbances also occur after experimental mild TBI in the absence of gross histological damage 7,10. In experimental models of concussion, these early metabolic and behavioral impairments recover over 3-10 days, depending upon age, injury severity and occurrence of repeat injuries 11,12.

Following human concussion, there is evidence of correlation between graded symptom checklist (GSC) scores and neurocognitive function (as assessed by both traditional pencil and paper as well as computerized neuropsychological testing). If these clinical parameters are taken as surrogate markers of ongoing cerebral dysfunction, then the majority of individuals appear to recover within 14 days of injury13,14.
In any case, both animal and human studies demonstrate clear physiological and behavioral disturbances of varying duration after concussive brain injury. While, in general, the timing of recovery falls within a range (rats 3-10 days; humans 7-14+ days), it is also clear that there is wide individual variation in the timing of recovery after concussion. This supports an individualized approach to concussion management and return to play.

b. Advanced Neuroimaging to Detect Concussion Pathophysiology

Neuroimaging has limited clinical use for diagnosing concussion. While sometimes used to rule out more severe intracranial pathology in cases of mild TBI, computed tomography is not useful to diagnose concussion. Numerous evidence-based algorithms provide good guidance for the use of CT in cases of mild TBI 15,16.

While macrostructural changes are not generally seen in concussion, concussion does induce functional impairments and microstructural changes, at least transiently. A growing number of research studies utilize advanced non-invasive imaging to detect differences between concussed and control groups. Positron emission tomography (PET) was one of the first advanced imaging methods to detect significant reductions in glucose metabolism in TBI patients, even those with mild TBI or concussion 17. There are also measures of post-concussive metabolic impairment, such as reduced N-acetylasparate (NAA) detected on magnetic resonance spectroscopy (MRS) that last up to 30 days, but have not been correlated with symptoms 18. However, in athletes who returned prematurely and sustained second concussions, the reductions in NAA lasted out to 45 days 18,19. Diffusion tensor imaging (DTI) shows abnormalities in diffusion along the pathways of white matter tracts. In some studies of concussion, the abnormalities on DTI corresponded to clinical measures of symptoms 20. Recently, studies of brain activation using fMRI have detected abnormalities in individuals with concussion 21,22, and perhaps more concerning, similar abnormalities have been reported in contact-sport athletes who did not report concussive symptoms, raising the possibility that subconcussive blows can result in cerebral dysfunction 23.

While research scans can show group differences between concussed athletes and uninjured athletes, such scans are not yet validated to use for individual patient management. Nonetheless it is a fact that concussion pathophysiology is detectable using advanced imaging modalities.

III. Post-concussive vulnerability:

a. Repeat concussions and acute biological vulnerability

Given our understanding of the pathophysiological cascade after concussion, it makes sense that the injured brain would be in a state of vulnerability. Many case reports raise concern about second impact syndrome (SIS), a catastrophic cerebral edema that has been reported after 2 concussive injuries in close succession, with incomplete recovery between 24. This entity has been called into question, as careful review of clinical cases often finds incomplete evidence of a definitive primary or secondary impact 25,26. In any case, there does not appear to be an epidemic of SIS cases in combatant sports like boxing or mixed martial arts (MMA), which clearly involve multiple repeated head impacts in a short period of time, suggesting that impact is only one factor contributing to the development of this syndrome.

Nonetheless, experimental models clearly show that repeated TBI can result in incrementally worse outcomes. This has been demonstrated using behavioral outcomes 27-29, metabolic measures 12,30,31 and axonal injury 28,29. Furthermore, the timing of repeat injuries may influence the magnitude of the impairment. Two studies showed that repeat TBI induced measurable metabolic deficits that were greater when the injuries were separated by <3 days, while injuries separated by 5 days appeared to act independently 12,31.

Clinical data do suggest that prior TBI is a strong risk factor for repeated concussions, and that those with a history of prior concussions are more likely to have a longer recovery after concussion 32. Furthermore, studies showed that among those athletes who experienced two concussions, the interval between the repeat concussions was <10 days in most cases (90%) 32,33. It has been hypothesized that this apparent vulnerability to repeat injury could be due to slowed reaction times, impaired cognitive processing and/or biological vulnerability related to the ongoing pathophysiology described above.

Thus, while the actual risk of SIS must be very low, there is considerable evidence that prior concussion is a risk for repeat concussion, and that the repeat concussions cause worse outcomes. The evidence supports keeping a concussed athlete away from contact risk activity while symptomatic based on a rationale to avoid repeat injury and worse/prolonged recovery.

b. Post-concussive neural activation and recovery
This is a complex issue. Experimentally there is evidence that intense brain activation acutely after brain injury may actually exacerbate the damage, as seen in paradigms of forced overuse or voluntary exercise. However, there is also evidence, particularly in the immature brain, that pharmacological blockade of excitatory neurotransmission after brain injury can also worsen the effects of injury or delay recovery. Interestingly, voluntary exercise instituted after a brief period (2 weeks), is no longer deleterious but actually promotes better recovery in adult rats. Clearly, there is a post-concussive ‘sweet spot’ in terms of intensity and timing of brain activation that can turn the switch from exacerbating the injury to enhancing recovery.

Anecdotal observation of patients demonstrates at least a subset of patients whose symptoms and/or cognition are worsened by excessive activity. However, there is also a potential detriment to indiscriminately keeping individuals outside of their normal daily activities (be it school or employment) for prolonged periods of time. Existing clinical data are sparse and fraught with caveats. A nonrandomized study of athletes who underwent a symptom free waiting period showed no reduction (and in fact a paradoxical increase) in the risk for repeat concussion in the athletes who underwent the waiting period compared to those who did not. In a retrospective study investigating self-reported levels of activity post-concussion, athletes with moderate amounts of activity reported the fewest symptoms and had the highest neurocognitive test scores, while those at either end of the activity spectrum (no activity or highest levels of activity) actually fared worse. A recent prospective study evaluating cognitive activity following concussion reported significantly longer recovery only in the quartile with the highest activity; the other 3 quartiles recovered similarly.

Recent human studies have also found abnormalities in functional brain activation in non-concussed contact sport athletes, as well as electrophysiological abnormalities in individuals decades after even a single concussion. The latter 2 studies, the individuals were not reporting symptoms at the time of imaging, further complicating the line between ‘subconcussive injury’ and ‘concussion’.

Evidence clearly supports protecting the concussed athlete from contact-risk activity. However, there is minimal evidence that complete inactivity improves recovery. Pharmacological inactivity may actually worsen outcomes, particularly in the developing brain. Moreover, there is some evidence that judiciously timed moderate levels of physical activity may actually help promote recovery.

c. Pediatric considerations in concussion recovery

Longstanding dogma holds that the younger brain is more resilient to injury. However, there is growing evidence that recovery from concussion takes longer in high school students (or younger) than college or professional athletes.

Experimental evidence demonstrates both resiliency and vulnerability after concussive injury in immature animals. Glucose metabolic disturbances after fluid percussion injury (FPI) are shorter in duration (3 days) in weanling rats than in adults (10 days). Profiles of calcium flux are different in the developing brain than the mature brain. Acute cell death is much less in weanling and juvenile animals than reported in adults. However, the ability of the young brain to respond to changes in its environment, dubbed experience-dependent plasticity, appears to be impaired after FPI. In addition, there is also experimental evidence demonstrating that unmyelinated fibers are more vulnerable to biomechanical injury than myelinated fibers. This would suggest incompletely myelinated, developing networks in the immature brain may be more sensitive to TBI.

Clinically, it is not readily possible to separate out the effects of age and level of play, since they often parallel each other. However, following concussion, high school football players performed more poorly than professional adult players on measures of reaction time and processing speed. There was also a trend toward longer recovery in the high school players. Two other comparative studies showed high school athletes with concussion had greater numbers of symptoms and longer duration of symptoms than collegiate athletes. The younger athletes also had longer duration of cognitive impairments on testing, and demonstrated persistent cognitive impairments at time points when symptoms had resolved. Imaging studies in young adolescents showed persistent reductions in cerebral blood flow (out to 30 days) and abnormalities in white matter diffusion (out to 4 months).

d. Repeated concussions and chronic cumulative impairment

There are few studies of repeat experimental TBI in developing animal models. As mentioned above, the time period of metabolic vulnerability appears to be shorter in younger age groups, however the immature brain also seems to be more vulnerable with regards to post-injury synaptic plasticity and white matter injury.
Adult animal models have also shown that TBI is capable of causing abnormal protein processing and deposition, which is one possible mechanism that may underlie chronic neurodegenerative changes seen long after repeated TBI 54-57. The exact cellular linkage between the acute neurometabolic cascade and these chronic changes in protein deposition is not known, and so it is difficult to speculate physiologically whether these changes are more worrisome following brain injury sustained during development. It does appear that the abnormal processing and deposition of proteins occurs after other acute injuries like ischemia58. In the setting of TBI, more repeated injuries over a longer duration of time would seem to place younger contact-sports participants at greater risk for chronic impairments and/or neurodegeneration.

The clinical evidence is fairly strong among professional athletes that increasing exposure to concussions or contact risk activity is associated with measurable chronic neurobehavioral impairments. In football, both memory problems 59 and depression 60 have been linked to greater exposure to concussions. Similar associations have been reported in professional boxers 61, jockeys 62 and soccer players 63.64. The apparent dose-response seen in these studies also supports a causal relationship. Retired NFL athletes have been reported to have approximately 3-fold increased risk of neurodegenerative cause of death compared to the general population65. There have also been a whole series of autopsy cases of ex-professional contact sports athletes where significant depositions of tau protein are seen in widespread brain regions; this has been termed chronic traumatic encephalopathy (CTE) 66-68. However, others have reported lower rates of ‘pure’ CTE, and higher occurrence of other causes of neurodegeneration76. The incidence of CTE among at-risk athletes is unable to be determined using case series, at least until a validated pre-mortem clinical marker is discovered. Just last year, a preliminary report showed increased brain tau using PET scanning in living retired NFL players69.

No longitudinal studies clearly identify that cognitive changes after repeat concussions are progressive. The concept of chronic neurocognitive impairment (CNI) has been introduced to indicate measurable deficits on neuropsychological testing without necessarily any evidence of neurodegenerative, in distinction to chronic traumatic encephalopathy (CTE), which is inferred to be degenerative 75.

Among amateur athletes, the evidence for chronic neurobehavioral impairment is less compelling and conflicting. Multiple studies reported an association between concussions and persistent cognitive impairment in amateurs 70,71, but other adequately powered studies did not 72,73. A 50-year follow-up study of high school football players found no difference in diagnosis of neurodegenerative disorder when compared to band members74. Further investigations are needed to determine whether younger individuals or those participating in amateur sports are at the same risk for chronic cumulative cognitive impairments as professionals appear to be.

This area of understanding chronic sequelae of concussion is one that is rapidly changing. There is evidence that greater contact-risk exposure in professionals is associated with later life neurobehavioral impairments. However, evidence is insufficient to determine whether there is a causative relationship between repeated concussions in amateurs and later dementia or psychiatric problems.

Reference List


