Chapter 12
Neuroimaging and Blood Biomarkers of Sport Concussion

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Introduction

Today, sports-related traumatic brain injury is more studied than ever before. Between 1.7 and 3 million concussions happen every year, of which around 300,000 are related to sports [25]. By nature of the injury, about 50% of concussions go unreported at time of presentation. Furthermore, without loss of consciousness, many athletes themselves are asked to self-report symptoms post-trauma, which may or may not happen [17]. Repeat concussions can have severe repercussions on the developing and developed brain, and scientific investigation has hoped to determine the best way of identifying traumatic brain injury when it takes place, both with imaging correlates and with blood biomarkers of injury that may distinguish injury in the hyperacute period. Concussion diagnostics are currently hampered by the lack of objective data. Research in sport-related concussion (SRC) is now moving towards more objectivity in both diagnosis and prognosis. In this chapter, we will discuss the current state of neuroimaging, fluid biomarkers, and their implications on where the field of sports-related concussion is moving.

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Neuroimaging in Sports-Related Concussion

Computed Tomography Imaging

For traumatic brain injury, the computed tomography (CT) scan is the first line imaging given its speed, cost, and ease of access. However, in relation to sports-related neurotrauma, the evidence clearly takes a divergent path**.** As SRC generally falls under the category of *mild uncomplicated TBI*, there are by definition no pathologic correlates seen on CT scan in concussion. It has been the consensus of multiple professional medical organizations that CT scan after acute sports-related concussion is not medically indicated. The American Academy of Neurology, for example, does not recommend the use of CT scan to *diagnose* a suspected sports-related concussion. However, mild *complicated* TBI is also possible with sports injury. These injuries, typically accompanied by "red-flag" symptoms, may require Emergency Department evaluation along with CT imaging. These symptoms may include loss of consciousness, post-traumatic amnesia, persistent Glasgow Coma Scale <15, focal neurologic deficit, evidence of skull fracture on examination, or signs of clinical deterioration [6]. It is important to note that while concussion and mild TBI are not indications for CT scans, neuroimaging in the aforementioned clinical context is to rule out moderate to severe traumatic brain injury, which may present with intracranial hemorrhage, cerebral contusions, or skull fractures depending on the mechanism and force of trauma applied to the skull. In consensus, the American Medical Society for Sports Medicine also states that CT scans should not be obtained unless the athlete in question demonstrates "worsening symptoms, pronounced amnesia, progressive balance dysfunction, or focal neurological deficits on examination," which may indicate signs of intracranial pathology, or "macrostructural" damage [8]. Similarly, the Centers for Disease Control present a variant of these guidelines, which are tailored to traumatic brain injury in the general population and take a more judicious approach to recommendations for CT scanning post TBI. These recommendations were adapted in part from early large multicenter cohort studies which attempted to determine clinical factors associated with the roughly 5–10% of patients with mild TBI who have positive imaging findings on CT [2, 16]. Furthermore, in relation to the pediatric population in which sports-related concussion is prevalent, there is evidence that CT scans in populations below 18 years of age was associated with an increased incidence of malignant and benign brain tumors [18, 19]. This further increases the need to limit arbitrary CT scans for straightforward presentations of SRC.

Magnetic Resonance Imaging

Athletes with concussion do not show structural lesions on CT and basic magnetic resonance (MR) imaging in the acute setting. However, Post-Concussive Syndrome is a well-studied and characterized phenomenon by which athletes may begin to

demonstrate a wide array of clinical symptoms such as psychological distress, cognitive impairment, and neurologic symptoms. Furthermore, recurrent concussion is posited to lead to a stepwise decline in neuropsychological functioning in affected athletes. The current guidelines from the American Association of Neurology recommend return to play when "signs and symptoms of concussion have resolved, are off of all medications (i.e., related to headache) and have been cleared by a qualified healthcare professional trained in the management of concussion, such as a neurologist" [6]. Unfortunately, it can be difficult to objectively determine when or if the symptoms have completely resolved. Due to the pathophysiology of concussion taking place in the functional level rather than the macro-structural level of the parenchyma, structural neuroimaging such as CT and MR logically tend to be *normal* in many athletes [4].

Advanced MRI Techniques

There is a vested interest on the part of clinicians and regulators to determine exactly who among concussed athletes will develop more severe symptoms. Recent studies have shown that patients with multiple concussions have an increased rate of extremity injury, advanced neurologic pathology, and neuropsychologic disorders such as depression, which may not present until later in life [14, 28]. The pathophysiology of concussion involves, among other things, changes in ion physiology within the brain, as well as pathologic microstructural changes. This mechanism makes certain MR sequencing uniquely suited to evaluating traumatic brain injury. Newer, advanced multimodal MRI technologies (Diffusion Tensor Imaging, Functional MRI, Susceptibility Weighted Imaging, and Magnetic Resonance Spectroscopy) are currently being studied for their value in discovering microscopic changes in the CNS environment secondary to concussion in athletes and the general population.

The main player in advanced MR imaging for SRC is *diffusion tensor imaging*. This is a modality of magnetic resonance that focuses on two variables. The first is *fractional anisotropy (FA)*, which is essentially the directionality of water movement within axon fiber tracts. The second variable is *mean diffusivity (MD)*, which informs about the total water content of the fiber tracts, irrespective of direction of flow [21]. This allows researchers to not only view fiber tracts but, in the case of sports-related concussion, evaluate the integrity of the fiber tracts on a molecular scale. The basis of this investigation is simple—normal functional white matter tracts have high FA, that is—directional flow down the axon to its target. This creates a portion of the characteristic DTI image of millions of thin string like tracts moving together. Normal functioning white matter will also have a low MD value, which indicates the diffusion of water *outside* of the axon tracts. Typically, MD is higher in damaged tissues as a result of increased free diffusion across damaged myelin, which subsequently inhibits ion gradient stabilization leading to ion outflow and water movement. In contrast, FA decreases due to the loss of coherence in the main preferred diffusion direction, such that water is no longer flowing down the axon to the terminal, but haphazardly causing the weighted average

movement in one direction to decrease. Damage to white matter tracts leads to alterations in this simple ratio. Studies into the areas of focal axonal disintegration have yielded evidence of decreases in FA and increases in MD in SRC patients acutely. These changes have been documented in the corpus callosum, corona radiata, temporal lobe, inferior longitudinal fasciculus, and internal capsule [1, 4, 27]. As a more practical example, decreased FA was seen in athletes who had a high frequency of heading (>855–1800 headings per year) in soccer. Strikingly, this finding was correlated with a lower cognitive function as tested by the CogState brief battery for mild TBI, suggesting that repeated "normal" head trauma had an effect on the integrity of axon tracts similar to that of concussion.

Fortunately, as DTI techniques have evolved and become more consistent, there has been a concerted effort to correlate the presence of DTI changes with changes in post concussive evaluation scales such as the Sports Concussion Assessment Tool. In one study in particular, investigators were able to show that SRC athletes' SCAT2 scores were able to predict the presence of DTI changes in the brain within 2 months of concussion [1]. Other studies have corroborated these findings, and correlated specific chronic SRC symptoms such as language, coordination, and visual deficits with anisotropic changes in the specific white matter tracts associated with those functions. Unfortunately, there is no consensus yet on the permanence of the microstructural changes seen in DTI imaging. There are data to suggest that microstructural changes may reverse between 2 days and 2 weeks post SRC, while others suggest a persistence of these changes as far out as 6 months to 3 years [9, 13, 15]. There is also evidence that recovery may be sex specific. One study demonstrated that the white matter changes seen on DTI were persistent for a longer period of time in female athletes who were part of a mixed gender study on SRC DTI changes [1].

In the last decade, functional MRI (fMRI) has emerged as a powerful tool for investigating changes in brain function with respect to SRC (Fig. 12.1). The underlying concept in fMRI is that resting neurons and active neurons differ in the amount of oxygen utilization, concomitant with their level of activity. As neurons increase activity, the level of deoxyhemoglobin present in the surrounding tissue should increase relative to non-active tissues. This activity results in an increase in paramagnetic deoxyhemoglobin, which can be quantified. This is known as blood oxygen level dependent imaging, or BOLD which is the lynchpin of fMRI sequencing [20]. The relative levels can then be compared between brain areas where functionally similar areas are said to have undergone "functional connectivity." Resting state (rs) fMRI studies over the last decade have demonstrated that athletes diagnosed with sports-related concussion show significantly altered functional connectivity within the first week post-injury [3, 30]. This is particularly significant, as this is the time during which most athletes are still symptomatic.

Further studies have demonstrated that this period of resting state functional impact persists well into the sub-acute phase to 1 month post-injury. This is particularly significant because this is generally when athletes are asymptomatic, demonstrating that functionally, neurons are still undergoing the process of repair [10, 29, 30].

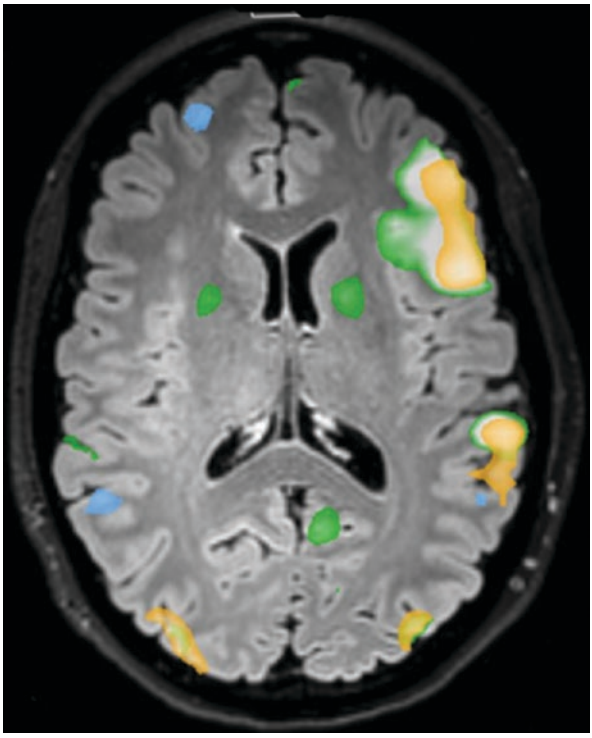

Fig. 12.1 Functional MRI study demonstrating left-sided language function

More recently, we have seen evidence of the underlying basis of many of the symptoms which typify concussion such as personality change [23], reaction time, as well as changes in the perception of pain. These have led to a particularly interesting finding. In 2014, Talavage et al. demonstrated in the study of SRC in population of high school athletes, fMRI had the ability to predict cognitive impairment in athletes that otherwise had no discernable symptoms of concussion. This deficit was linked to the dorsolateral prefrontal cortex [24], and markedly elevated in players who saw regular helmet-to-helmet contact such as lineman and defensive backs.

Other MR sequences have been investigated for potential use in SRC. Magnetic resonance spectroscopy (MRS), which has been used to evaluate intracranial tumors, has demonstrated changes in neuronal metabolism which may last weeks after initial injury, especially in the hippocampus and primary motor cortices [9, 26]. Studies have shown that there is a decrease in N-acetylasparate (NAA) in white matter after SRC. However, as neurometabolic changes can be dependent on many factors which are not always controlled, the value of these findings is not yet understood. High-resolution T1-weighted MR imaging is capable of providing highly detailed anatomical images of the brain and some studies have indicated that some athletes who have been cleared to play demonstrate evidence of parenchymal atrophy [7]. However, since the advent of DTI, the use of

standard T1 imaging has not been as thoroughly investigated, as it does not reveal information about the likely microstructural changes taking place.

Blood Biomarkers for Sports-Related Concussion

Macro-structural imaging correlates, as described previously in this chapter, may not indicate the extent of the injury within the first few hours of trauma, which may lead to delayed care. Microstructural imaging such as DTI, fMRI, and MRS have not yet been approved for regular use in acute sports-related concussion. It is for this reason that the current research into blood biomarkers associated with trauma is expanding. One of the primary responses to acute traumatic brain injury is an acute inflammatory response mediated by cytokine release. In response to this injury, there is local breakdown of the blood brain barrier, which allows the normally isolated CNS milieu to interact with the serum. Thus, markers of damage may become present in the serum or plasma. The benefit of this pathophysiology is that diagnosis, risk stratification, and treatment of TBI could potentially be detected in a relatively simple fashion, as opposed to biomarkers in cerebrospinal fluid, or imaging techniques, which may be expensive and time consuming. However, given the individual variability in presentations, low quantity of TBI biomarkers in blood, variability in clearance rates of biomarkers, and several other reasons, there has not been a clinical role for blood biomarkers in clinical practice so far. Improvements in the reliability of biomarker assays have been instrumental in the recent advances in the field. There are several blood biomarkers currently under investigation in relation to SRC, which can grossly be categorized into biomarkers of neuronal, axonal, or astroglial injury (Fig. 12.2).

Neuronal Injury

Biomarkers for neuronal injury include ubiquitin C-terminal hydrolase-L1 (UCH-L1) and brain derived neurotrophic factor (BDNF), amongst others. UCH-L1, a protein found in neuronal cytoplasm, has been well studied in TBI. However, it is also present in peripheral nerves and other non-CNS organs. In severe TBI, increases in UCH-L1 have been shown consistently. In mild TBI, UCH-L1 has been shown to have the ability to predict the likelihood of a positive CT scan with a traumatic intracranial lesion. However, its utility in CT-negative mild TBI is less certain. Other neuronal markers such as BDNF and neuron-specific enolase (NSE) have demonstrated little success in the diagnosis or management of SRC.

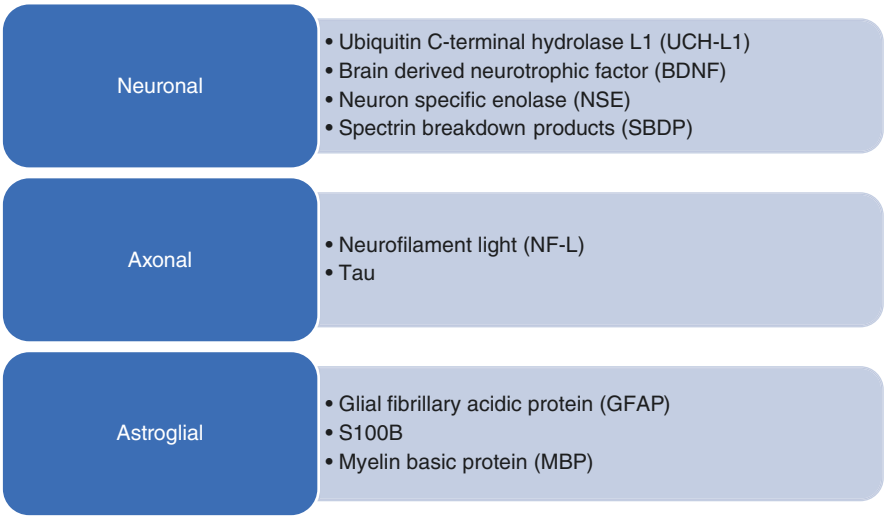

Fig. 12.2 Categories of blood biomarkers for sports related concussion

Axonal Injury

The most promising biomarkers for axonal injury include tau protein and neurofilament-light (NF-L). Tau is a microtubule-associated protein which is responsible for microtubule stabilization in the milieu of the cell. This protein is especially important within axons, in which it is utilized to transport neurotransmitter vesicles down the axon to the terminal. Aggregation of tau protein in the general population has been implicated as the inciting factor in the initiation of the neuropathology of Alzheimer's disease [11, 22]. Tau has been most notably implicated in the presence of chronic traumatic encephalopathy, the step-wise degeneration of cognitive function seen in repeated cranial trauma in boxing and other contact sports with high velocity head trauma [5]. Tau has also been investigated as a possible biomarker for TBI. Investigation of Olympic athletes after rounds of boxing in 2012 demonstrated that there were elevations in the levels of tau in these patients, although there were no symptoms of concussion. Serum tau has also been shown to rise in concussed hockey players, and was shown to predict time to return-to-play. Neurofilament-light is a significant component of the axonal skeleton. A study of collegiate football players found that concentrations of NF-L increased over the course of a season. Furthermore, elevations in serum NF-L were found starting at 1 hour post-injury, and its elevations were correlated to time to return-to-play. Further studies have shown that NF-L is able to accurately distinguish acute SRC from controls. Other less well-studied axonal proteins include breakdown products of alpha-2 spectrin.

Astroglial Injury

Markers of astroglial injury include glial fibrillary acidic protein (GFAP) and S100-B. S100ß protein's primary function is to bind and regulate intracellular calcium levels within astrocytes. It has been demonstrated by several groups that there are physiologic increases in the serum level of S100ß with simple physical exertion. However, in the case of acute concussion, elevations in its levels have been demonstrated to forewarn the presence of intracranial hemorrhage within closed head injury patients [12]. GFAP is one of the most well-studied proteins in TBI. It is an intermediate filament protein found in astrocytes and has been shown to be able to detect mild TBI, and may be more specific than other biomarkers. In SRC specifically, GFAP is able to distinguish symptomatic athletes with high accuracy. However, other studies have not replicated these results.

Future of Blood and Imaging Biomarkers in SRC

SRC is a difficult clinical diagnosis due to patient heterogeneity in presentation, reliance on self-reporting, lack of patient education, and variability in providers, amongst other reasons. A move toward more objective data is necessary in order to achieve large-scale improvements in clinical outcomes of SRC. Both blood and imaging biomarkers continue to be an area of intense interest in SRC due to their objectivity. However, research in biomarkers has continued to be hamstrung by a reliance on clinical diagnosis of SRC as a benchmark. Numerous studies have demonstrated that asymptomatic athletes without clinical diagnosis of SRC show biomarker evidence of brain injury [24]. The cause of this is unclear. In addition, many of the studies cited here demonstrate statistically significant changes in biomarkers, but the within-subject variability is extreme. This greatly limits the current practicality of biomarker tests for clinical use today. Nevertheless, it is anticipated that improvements in imaging techniques and fluid assays may help circumvent these issues in the future.

Conclusion

Advanced neuroimaging techniques and blood biomarkers hold great promise for the future of SRC diagnosis and management. It is anticipated that they will eventually become a part of standard clinical practice. Further research is needed prior to the realization of this goal.

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