Imaging the Role of Myelin in Concussion

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KEYWORDS

• Myelin water imaging • Mild traumatic brain injury • White matter • Brain

KEY POINTS

- Myelin water imaging (MWI) provides mild traumatic brain injury (mTBI) researchers with a specific myelin biomarker and helps to further elucidate microstructural and microarchitectural changes of white matter after mTBI.
- Ongoing improvement of scanner hardware and software with the implementation of MWI across scanner platforms will likely result in increased research regarding the role of myelin in traumatic brain injury.
- Initial results show altered myelin 2 weeks after concussion and normalization by 2 months after injury.

INTRODUCTION

Myelin, the fatty substance that surrounds, protects, and electrically insulates axons in the central nervous system, is thought to play an important role in the pathophysiology of mild traumatic brain injuries (mTBIs).[1,2] White matter tracts (both myelinated and nonmyelinated axons) are vulnerable to damage from the impact-acceleration forces sustained in a traumatic brain injury (TBI), with evidence indicating that nonmyelinated axons are more vulnerable than myelinated ones.[3] Further evidence suggests that damage to either the axon or myelin sheath alone can lead to damage to the other.[4,5] This damage occurs from diffuse shear strains caused by linear and rotational acceleration of the brain during blast impacts. As opposed to more severe TBI, in which complete axon severance is observed following high-magnitude impacts, it is thought that axonal and myelin disorder in mTBI takes days to weeks to develop.[6–10] After primary axonal shearing and stretching, and possible blood capillary ruptures,[6] a cascade of secondary mechanisms takes place through biochemical, metabolic, and cellular changes.[10] Briefly, these changes include an increased sodium influx, which results in a continuously working sodium-potassium pump to restore the resting state of the neurons. More energy in the form of adenosine triphosphate is required and this is measurable through an increased blood flow. During the acute stage of mTBI, around 48 hours, the brain first experiences this increased blood flow and is able to compensate for the high energy demand.[10] However, shortly afterward, over the subsequent 24 hours, the cerebral perfusion becomes diminished, leading to an insufficient energy supply.[10] This reduction in global and regional blood flow has been linked to recovery duration,[11] with some work suggesting a subsequent oxidative stress

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accumulation that results in suppression of the differentiation of oligodendrocyte precursor cells to oligodendrocytes, as well as myelin renewal.[12] This process in turn is expected to lead to a loss of oligodendrocytes and demyelination of the axons.[2,5,13] A second injury during this vulnerable period of reduced blood flow can result in even more serious injuries.[14] Along with the ionic flux, indiscriminate glutamate release occurs, leading to mitochondrial dysfunction and calcium sequestration, further exasperating the energy crisis and causing cytoskeletal damage.[10] Damage to the myelin and oligodendrocytes can occur through this calcium overload in the cytoplasm.[15] Swelling of the axon caused by impaired transport can lead to axonal disconnection and wallerian degeneration (anterograde degeneration).[6,16] These observations have been seen in histopathology specimens, showing axonal bulbs, irregular tortuous axonal swellings, and small sections of degraded myelin sheaths.[1,17,18]

Myelin Damage in Mild Traumatic Brain Injury

Myelin damage observations in mTBI have come in the form of decompaction, fragmentation, and complete degradation.[1,17,19–22] A study by Johnson and colleagues[19] provided evidence for myelin degeneration and active phagocytosis of myelin fragments in humans following moderate/severe TBI. Donovan and colleagues[23] showed that repeated mTBI in rats leads to a spectrum of changes, including separation of the myelin sheath from the axon, decompaction of the myelin sheath, and fragmentation of the myelin sheath. In addition, investigations of secondary degeneration in the optic nerves of rats, which characterize ongoing changes associated with neurotrauma, have shown that myelin is particularly susceptible to secondary damage.[24,25] Payne and colleagues[25] found a maximum of 15% of myelin sheaths to be decompacted in rats following secondary degeneration. This damage is caused because myelin's compact layers of lamellae are held together with proteins that are vulnerable to damage from reactive oxidative species and lipid peroxidation from secondary degeneration,[26] processes that are known to occur following mTBI.[27,28] Thus, there is circumstantial evidence to support myelin decompaction, a mixture of decompaction and degeneration, and degeneration alone, following mTBI.

Although these findings have been observed in animal models and postmortem human studies, dynamic in vivo studies of myelin damage directly observed in the human brain have been few. A better understanding of myelin damage of humans in vivo, in the setting of mTBI, could lead to greater insights into the pathophysiology and cognitive/behavioral outcomes, and could greatly improve diagnosis and allow the tracking of brain changes over the recovery period. In addition, it could serve as a marker in therapeutic studies, and may provide novel opportunities for interventional treatments.

IMAGING MYELIN

Diffusion Tensor Imaging

One such attempt at in vivo myelin examination is through diffusion tensor imaging (DTI). DTI is an advanced MR imaging technique that uses magnetic gradients to measure water diffusion in the brain, and, in turn, brain microstructure. This measurement is accomplished by modeling the diffusion data using a symmetric rank-2 positive tensor,[29] which in turn can give information on the amount of diffusion, main direction, and degree of anisotropy. The most commonly reported measures from DTI include mean diffusivity, relative anisotropy, fractional anisotropy (FA), fiber direction maps, and three-dimensional fiber tractography,[30] with FA being the most commonly reported value. Thus, DTI has provided a highly sensitive window into tissue microstructure and changes in white matter, greatly improving understanding of the pathophysiology of mTBI. Although not always in agreement, the most consistently implicated structures affected in mTBI have been the genu of the corpus callosum,[31] the cingulum bundle, the anterior corona radiata, the uncinate fasciculus, and the superior longitudinal fasciculus.[32] Although DTI can detect microstructural changes of white matter that other conventional imaging methods cannot, it lacks the specificity required to identify the parts of the white matter that are being affected, such as the axonal membrane, myelin sheath, or other elements of the microstructure and microarchitecture. For example, Beaulieu and Allen[33] reported in 1994 a similar degree of measured anisotropy in both nonmyelinated olfactory and myelinated trigeminal nerves, showing that myelination is not necessary for diffusional anisotropy. Studies such as these have illustrated the risks of interpreting DTI data as representing white matter changes caused by myelin.[34]

Magnetization Transfer

Another MR imaging method that has been suggested to give insights into changes in myelin is magnetization transfer (MT). MT uses off-resonance excitations to measure magnetization transfer of hydrogen within myelin with