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Review

White matter involvement after TBI: Clues to axon and myelin repair capacity

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ABSTRACT

Impact-acceleration forces to the head cause traumatic brain injury (TBI) with damage in white matter tracts comprised of long axons traversing the brain. White matter injury after TBI involves both traumatic axonal injury (TAI) and myelin pathology that evolves throughout the post-injury time course. The axon response to initial mechanical forces and secondary insults follows the process of Wallerian degeneration, which initiates as a potentially reversible phase of intra-axonal damage and proceeds to an irreversible phase of axon fragmentation. Distal to sites of axon disconnection, myelin sheaths remain for prolonged periods, which may activate neuroinflammation and inhibit axon regeneration. In addition to TAI, TBI can cause demyelination of intact axons. These evolving features of axon and myelin pathology also represent opportunities for repair. In experimental TBI, demyelinated axons exhibit remyelination, which can serve to both protect axons and facilitate recovery of function. Myelin remodeling may also contribute to neuroplasticity. Efficient clearance of myelin debris is a potential target to attenuate the progression of chronic pathology. During the early phase of Wallerian degeneration, interventions that prevent the transition from reversible damage to axon disconnection warrant the highest priority, based on the poor regenerative capacity of axons in the CNS. Clinical evaluation of TBI will need to address the challenge of accurately detecting the extent and stage of axon damage. Distinguishing the complex white matter changes associated with axons and myelin is necessary for interpreting advanced neuroimaging approaches and for identifying a broader range of therapeutic opportunities to improve outcome after TBI.

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1. Introduction

Impact-acceleration forces to the head are the most common cause of traumatic brain injury, whether in the context of accidents, sports, or military service. White matter tracts are particularly vulnerable to damage from impact-acceleration forces. Accordingly, symptoms from mild to moderate TBI correlate with neural circuit deficits expected from the disruption of myelinated pathways. While this overall understanding of white matter involvement in TBI is widely recognized, white matter must be examined across whole brain, tract, cellular, and molecular levels to improve diagnostic measures, predict outcomes, and develop therapeutic interventions that maximize repair capacity. This review will work across these levels while focusing on parameters

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of axon and myelin integrity following TBI, including features specific to the capacity for myelin repair and recovery of axon function.

1.1. White matter injury is a major component of TBI

White matter atrophy dramatically demonstrates significant white matter involvement in moderate–severe forms of TBI in patients who survive to a chronic post-injury stage (Tomaiuolo et al., 2004; Bendlin et al., 2008; Kim et al., 2008; Sidaros et al., 2009; Green et al., 2014). White matter atrophy is often accompanied by overall atrophy of the brain as well as ventricular enlargement (Bigler et al., 2013; Green et al., 2014). Within the corpus callosum, atrophy is present in 63–86% of severe TBI cases based on comparison of MRI scans taken at approximately 5 and 20 months post-injury (Green et al., 2014). White matter atrophy associated with cortical atrophy has a low probability of repair, due to the loss of neuron cell bodies in the corresponding gray matter regions. In the face of neuron cell death, pathological consequences to the axon and myelin are uniformly degenerative. In contrast, this review will focus on damage to axons and myelin that initiates within white matter tracts. Distinct pathological processes involving axons and myelin will be discussed relative to indications of potential for repair, especially in milder forms of TBI.

The predominant concern with white matter injury from TBI is traumatic axonal injury (TAI). Long axonal projections that traverse the brain in white matter tracts are damaged from forces of torsion, tension, and compression in impact-acceleration injuries to the head. TAI occurs in a pattern of damaged axons distributed among adjacent intact axons within the white matter (Fig. 1). Experimental models indicate that TAI does not necessitate death of the corresponding neuron cell body (Greer et al., 2011; Wang et al., 2013). In more severe forms of TBI, TAI occurs in multiple neuroanatomical regions and is defined clinically as diffuse axonal injury (DAI). The severity of DAI is classified based on the areas of white matter with TAI, as determined from neuropathological evidence of axon damage (Adams et al., 1989) or neuroimaging (Kim and Gean, 2011). Grade I DAI involves lesions in areas of gray matter–white matter junctions in the corona radiata. Grade II DAI includes Grade I lesion sites as well as the corpus callosum, with extension from the splenium toward the genu with increasing severity. Grade III DAI involves these sites with the addition of brainstem tracts.

1.2. Challenges of clinical detection of white matter injury across the spectrum of TBI severity

Neuroimaging detection of hemorrhages within white matter tracts has become interpreted as indicative of concurrent TAI. However, only 10% of closed head trauma patients demonstrate admission CT scans with petechial hemorrhages in the gray–white matter junctions associated with TAI while approximately 80% of TAIs are non-hemorrhagic and better detected with MRI (Gentry et al., 1988; Kim and Gean, 2011). Postmortem analysis confirms that severe TBI cases exhibit axon damage with hemorrhagic lesions (Oppenheimer, 1968; Blumbergs et al., 1995). However, axon damage often occurs in the absence of vascular damage in mild TBI and is found even in some cases of severe TBI (Oppenheimer, 1968; Blumbergs et al., 1995). These findings have been interpreted as indicating that axons are more vulnerable than blood vessels to damage from TBI (Blumbergs et al., 1995). Animal models using milder forms of impact-acceleration brain injuries have provided mechanistic support that axon damage can occur without vascular damage based on analysis from gross pathology, histological staining, or MRI (Povlishock et al., 1983; Jane et al., 1985; Povlishock, 1993; Sullivan et al., 2013).

Advanced MRI techniques are attempting to more sensitively and accurately detect the extent of white matter damage in patients with mild TBI. Diffusion tensor imaging (DTI) generates additional information from MRI sequences that detect changes in anisotropy, which is particularly advantageous for analysis of highly anisotropic myelinated nerve fibers that align within white matter tracts. DTI can be used to interpolate the pathways of fiber bundles so that abnormal findings may indicate disrupted pathways. However, the inherent limitations of DTI tractography measures for anatomical accuracy must be recognized to appropriately interrogate white matter pathways for comparative changes in microstructure (Thomas et al., 2014). Tractography estimates from voxels that are averaged on the scale of MRI measurements have limited accuracy for differentiating changes in fiber orientation,

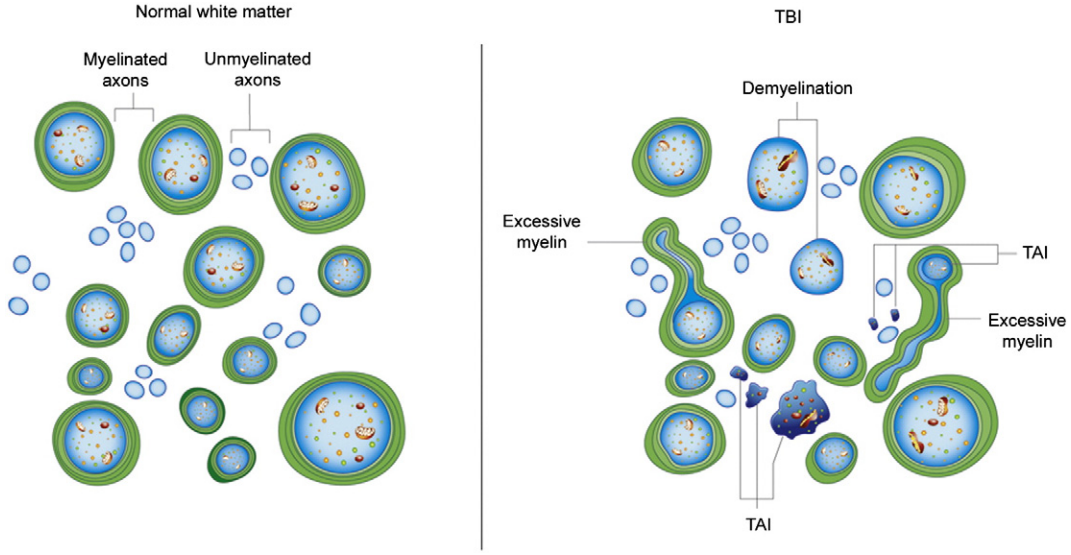

Fig. 1. Milder forms of TBI may cause complex pathology of axons and myelin, rather than the overt white matter loss resulting from more severe TBI. A: Cross section view of white matter illustrates a set of normal myelinated and unmyelinated axons. Axons are shown in blue and myelin in green. B: The same set of axons illustrates multiple aspects of damage after TBI. Traumatic axonal injury (TAI) is characterized by a pattern of degenerating axons dispersed among intact fibers. Unmyelinated axons are particularly vulnerable to degeneration after TAI. TAI also causes degeneration of myelinated axons. The myelin sheath collapses as the axon degenerates but is slow to degrade in the CNS. In addition, the dispersed white matter axons damaged by TAI may be a subset of only one or two axons among a cohort of 20 or more axons ensheathed by a surviving oligodendrocyte. This mismatch of axon integrity among the cohort may dysregulate myelin maintenance signals to the oligodendrocyte, resulting in aberrant myelin synthesis. A combination of effects may explain the long excessive myelin figures observed in models of mild TBI. Separate from the axons undergoing TAI, viable axons may also lose function due to demyelination.