Acute and chronic traumatic brain injury: Pathophysiology and treatment

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Acute damage produced by traumatic brain injury (TBI) can evolve into chronic neurodegeneration. MRI studies show rapid cortical and thalamic atrophy after a single experimental TBI. In contrast, white matter atrophy is either rapid or delayed. Atrophied white matter has damaged microstructure as seen by diffusion tensor MRI. Delayed atrophy produces modest changes in diffusion tensor parameters suggesting a yet unknown microstructural compensation. Injured gray and white matter develop perinuclear phosphotau aggregates found exclusively in oligodendrocytes. Thalamic phosphotau aggregates develop amyloidogenic β-sheets suggesting increased pathogenicity. These data suggest a single head impact produces multiple forms of chronic, progressive neurodegeneration.

TBI increases the risk of developing Parkinsonian-like symptoms. A single impact induces atrophy in caudate putamen, substantia nigra and globus pallidus. Substantia nigra pars compacta has a partial loss of dopaminergic neurons; substantia nigra pars reticulata and internal capsule accumulate phospho-α-synuclein. These pathological changes likely underlie movement deficits that appear in mice months after injury. These data suggest that mice develop Parkinsonian-like symptoms after a single experimental TBI.

The complex pathophysiology of TBI suggests that no single drug will have sufficient efficacy for treatment. The combination of two FDA-approved drugs, minocycline and N-acetylcysteine improves histological, electrophysiological cognitive and motor deficits in two rodent TBI models. The combination retains substantial efficacy when first dosed at 12 or 72 hours post-injury. Twelve-hour dosing of the combination lowers serum phosphotau levels. This provides a therapeutic endpoint for a phase 2 clinical trial being proposed to the NIH NeuroNext Clinical Trial Network.