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Review article

White matter injury in ischemic stroke

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ABSTRACT

Stroke is one of the major causes of disability and mortality worldwide. It is well known that ischemic stroke can cause gray matter injury. However, stroke also elicits profound white matter injury, a risk factor for higher stroke incidence and poor neurological outcomes. The majority of damage caused by stroke is located in subcortical regions and, remarkably, white matter occupies nearly half of the average infarct volume. Indeed, white matter is exquisitely vulnerable to ischemia and is often injured more severely than gray matter. Clinical symptoms related to white matter injury include cognitive dysfunction, emotional disorders, sensorimotor impairments, as well as urinary incontinence and pain, all of which are closely associated with destruction and remodeling of white matter connectivity. White matter injury can be noninvasively detected by MRI, which provides a three-dimensional assessment of its morphology, metabolism, and function. There is an urgent need for novel white matter therapies, as currently available strategies are limited to preclinical animal studies. Optimal protection against ischemic stroke will need to encompass the fortification of both gray and white matter. In this review, we discuss white matter injury after ischemic stroke, focusing on clinical features and tools, such as imaging, manifestation, and potential treatments. We also briefly discuss the pathophysiology of WMI and future research directions.

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Abbreviations: AD, axial diffusivity; ADC, apparent diffusion coefficient; ADMSC, adipose-derived mesenchymal stem cell; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ATP, adenosine triphosphate; BAEP, Brainstem auditory evoked potential; BBB, blood brain barrier; BMSC, bone marrow stromal cells; BOLD-fMRI, blood oxygen-level dependent functional MRI; Ca^{2+}, calcium ion; CMCT, central motor conduction time; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computer tomography; DKI, diffusion kurtosis imaging; DTI, diffusion tensor imaging; DW-MRI, diffusion-weighted magnetic resonance imaging; DWI, diffusion-weighted imaging; EEG, electroencephalography; FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery; fMRI, functional magnetic resonance imaging; GFAP, glial fibrillary acidic protein; GluRs, glutamate receptors; GM, gray matter; GMI, gray matter injury; HUSBC, human umbilical cord blood cells; IL-6, interleukin-6; IL-18, interleukin-18; MBP, myelin basic protein; MCA, middle cerebral artery; MCP-1, monocyte chemotactic protein 1; MD, mean diffusivity; MEP, motor evoked potential; MMP-9, matrix metalloproteinase 9; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MT, magnetization transfer; MTR, magnetization transfer ratio; NFL, neuroinflament light polypeptide; NIHSS, National Institutes of Health Stroke Scale; NMDA, *N*-methyl-D-aspartate; OPCs, oligodendrocyte progenitor cells; RD, radial diffusivity; rMT, resting motor threshold; ROS, reactive oxygen species; rTMS, repetitive transcranial magnetic stimulation; r-tPA, recombinant tissue-type plasminogen activator; SEP, somatosensory evoked potential; SBP, systolic blood pressure; sICH, symptomatic intracerebral hemorrhage; SMART-MR, Second Manifestations of ARTerial disease-Magnetic Resonance; TABASCO, Tel Aviv Brain Acute Stroke Cohort; TMS, transcranial magnetic stimulation; WM, white matter; WMI, white matter injury; Zn^{2+}, zinc ion.

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1. Introduction

The mammalian neocortex is a sizeable structure with lamellar architecture and enlarges rapidly during early development. During primate evolution, the neocortex expanded greatly in size and this was paralleled by improvements in cognitive function. For example, the sum of neocortical gray matter (GM) and nearby white matter (WM) occupies only 10% to 20% of whole brain volume in insectivores, but accounts for 80% of whole brain volume in humans (Zhang and Sejnowski, 2000). According to neuroimaging studies, the volume of WM is $456 \pm 48\,cm^3$ in men and $392 \pm 42\,cm^3$ in women, which accounts for ~40% of total human brain volume (Pausova et al., 2007). The majority of WM tracts communicate across cortical areas and the rest join the cortex with subcortical structures. As the size of the brain enlarges during development, the WM immediately below the cortex expands disproportionally faster than cortical GM in order to unite distant cortical regions. Similar to GM, WM is critically dependent on a continuous supply of oxygen and glucose. However, WM receives less collateral circulation than GM and has a smaller blood supply, leading to extreme susceptibility to ischemia. Therefore, ischemic stroke rapidly and profoundly damages WM.

In the ischemic environment, glutamate and adenosine triphosphate (ATP), two major excitatory neurotransmitters, play pivotal roles in the pathophysiologic cascades of white matter injury (WMI) after stroke. Glutamate and ATP lead to inflammation and oxidative stress (Matute and Ransom, 2012) and eventually induce oligodendrocyte death, axonal demyelination, WM structural damage, and neurobehavioral disorders (Lo et al., 2003). Hence, both gray matter injury (GMI) and WMI contribute significantly to neurological dysfunction in stroke. Preclinical and clinical studies of stroke have emphasized GMI over WMI, perhaps contributing to the failures of neuroprotectants designed to target neuronal death pathways (Ho et al., 2005; Wang and Shuaib, 2007). Thus, there is an urgent need for additional basic and clinical research on WMI, in the context of the entire brain as a sensitive organ system with highly heterogeneous cellular constituents.

2. Anatomy of WM

The principal components of GM include neuronal cell bodies, dendrites, and axons for local information processing, whereas WM mainly contains long extensions of myelinated and unmyelinated axons that are organized into tracts and surrounding glial cells and blood vessels. WM is classified into *periventricular WM* and *deep WM* based on anatomical location. Periventricular WM is found immediately adjacent to the ventricles (within ~1 cm) whereas deep WM is distinctly isolated from the ventricles and found beneath the cortex (Scheltens et al., 1992). WM tracts can be divided into three major categories according to their connectivity and functionality: (1) projection fibers—ascending and descending tracts connecting parts of the cerebral cortex and subcortical