REVIEW

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White Matter Injury in Central Nervous System Disorders

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Abstract: As the aging process accelerates and living conditions improve, central nervous system (CNS) diseases have become a major public health problem. Diseases of the CNS cause not only gray matter damage, which is primarily characterized by the loss of neurons, but also white matter damage. However, most previous studies have focused on grey matter injury (GMI), with fewer studies on white matter injury (WMI). In this article, we will briefly describe the structure and function of white matter, summarize the pathological changes of WMI, and focus on the molecular mechanisms and therapeutic research advances in WMI after ischemic stroke, cerebral hemorrhage, Alzheimer's disease, and multiple sclerosis diseases.

Keywords: white matter injury, central nervous system, oligodendrocytes, myelin

Basic Characteristics of White Matter and Its Role

The human brain is composed of white and gray matter, with white matter accounting for about 40-50% of the volume of the human brain. Imaging studies have shown that the volume of white matter is approximately 456 ± 48 cm³ in males and $392 \pm$ 42 cm³ in females.¹ White matter consists of myelinated and unmyelinated axons and glial cells, including myelin-producing oligodendrocytes (OLs), microglia, astrocytes and oligodendrocyte progenitor cells (OPCs). It also contains neural networks formed by axon bundles to mediate basic connections between different key motor and cognitive cortical areas. Myelin acts as an electrical insulator for axons and is responsible for the rapid propagation of impulses and protection of nerve fibres from injury.^{2,3} OLs are myelin-producing cells responsible for axonal myelin formation under normal conditions and myelin regeneration after axonal injury. Astrocytes are the most heterogeneous and abundant glial cell type in the CNS and play an important role in maintaining homeostatic balance and influencing myelin formation.⁴

White matter is divided into periventricular white matter and deep white matter based on anatomical location.⁵ The periventricular white matter is adjacent to the ventricles, whereas the deep white matter is separated from the ventricles and lies below the cortex. Deep white matter has low blood flow and almost no collateral circulation supply; vascular autoregulation is poorer within the white matter region than in grey matter; and inflammation-responsive glial cells are abundant and inflammatory responses are intense within the white matter region. Notably, even in the normal aging process, there is a decline in the total length of white matter at a speed of approximately 10% each decade.^{6,7} OLs, especially OPCs, are highly sensitive to ischaemia-induced oxidative stress, excitotoxicity and inflammation, leading to OLs death and WMI after brain injury.⁸ When brain tissue is damaged, even if only a single OLs is damaged, it may cause damage to multiple neuronal axons, thus affecting neurological function.⁹ The above characteristics suggest that white matter may be more vulnerable to damage than grey matter. Therefore, further attention to white matter damage is critical.

Mechanisms of White Matter Damage

Neuroinflammation

Neuroinflammation is considered to be a balanced inflammatory response that is important in the intrinsic repair process following injury or infection. In the chronic state of disease, injury, or infection, persistent neuroinflammation leads to an increase in cytokines, chemokines, and reactive oxygen species, resulting in tissue damage.¹⁰ Most neurological diseases are accompanied by an increased neuroinflammatory response. When brain or spinal cord injury occurs, microglia and astrocytes respond rapidly, and microglia polarise into two phenotypes, M1 and M2, with M1 playing a pro-inflammatory role and releasing inflammatory factors (tumor necrosis factor α , inducible nitric oxide synthase), and M2 playing an anti-inflammatory role and releasing trophic factors (interleukins-10, transforming growth factor β) to promote the repair of white matter damage.¹¹ Inflammatory factors released in response to inflammation also promote oligodendrocyte death to exacerbate white matter damage.

Ischaemia and Hypoxia

Cerebral hypoxia-ischemic episodes cause cellular depolarization, cellular edema, reactive oxygen species production, and endothelial dysfunction, leading to neuronal and glial cell damage. Cell swelling occurs as early as 30 min after arterial occlusion, and large numbers of OLs die within 3 h.¹² Studies have shown that 30 minutes of oxygen-glucose deprivation results in 90% of OLs dying within 9 hours.¹³ OLS has important implications for myelin production, and pathology of OLs leads to demyelination and myelin dysplasia, which have profound effects on axonal function, transport, structure, metabolism, and survival.¹⁴ Therefore, ischemia and hypoxia leading to OLs damage is one of the important mechanisms of white matter damage.

Glutamate Excitotoxicity

Glutamate excitotoxicity is one of the major factors in CNS ischemic injury.¹⁵ In the mature healthy brain, glutamate is released from presynaptic neuronal endings into synapses via cytokinesis and binds to postsynaptic ionotropic (NMDA, AMPA, and erythrocyanine receptors) and metabotropic glutamate receptors, inducing a Ca^{2+} mediated signaling cascade leading to normal physiological cellular responses; During excitotoxicity, increased neuronal release and decreased uptake by astrocytes lead to elevated extracellular glutamate levels, resulting in postsynaptic glutamate receptor over-activation, Ca^{2+} overload, and activation of apoptotic pathways, leading to demyelination, axonal damage, and death of OLs, resulting in white matter damage.^{16,17}

White Matter Injury and Ischaemic Stroke

Characteristics and Mechanisms of Injury in WMI After Ischaemic Stroke

Stroke is one of the leading causes of disability and death worldwide. It is well known that ischaemic stroke can cause grey matter damage. However, ischaemic stroke can also cause severe WMI, which is a risk factor for poorer stroke prognosis and poor neurological outcome. Age is one of the most important risk factors for ischaemic stroke and with the risk of stroke dramatically increasing with age.¹⁸ However, the efficiency of myelin regeneration in white matter lesions decreases with age.¹⁹ As the world's population continues to age, it is likely that the prevalence of stroke will increase, and as a result the incidence of WMI will go up with it. WMI is a key component of ischaemic injury, and ischaemic stroke-induced WMI leads to long-term sensory-motor and cognitive deficits.

The integrity of the normal appearance of white matter may be a marker of "brain reserve properties", which are closely related to cognitive function. In a cohort study of acute cerebral stroke, 142 patients with mild to moderate stroke or transient ischaemic attack underwent Magnetic Resonance Imaging (MRI) within seven days of stroke. One year later, the patients were reassessed for cognitive function and it was found that patients who already had a WMI that existed one year earlier were more likely to have cognitive dysfunction and this was independent of the volume and location of the ischaemic lesion.²⁰ Animal studies have found that WMI occurs on day 7 after ischaemic stroke and then gradually recovers from day 7 to day 30.²¹ Among the Diffusion Tensor Imaging (DTI) parameters, Fractional Anisotropy (FA): FA reflects the anisotropy of water molecules diffusing in the tissue. The higher value of FA represents the more directional diffusion of water molecules in the tissue, which indicates the better connectivity of the nerve fiber bundles. Mean Diffusivity (MD): MD reflects the average speed of diffusion of water molecules in the tissue, the higher the MD value, the faster the diffusion of water molecules, the more obvious the destruction of microstructure in the tissue. Radial Diffusivity (RD) and Axial Diffusivity (AD): RD and AD indicate the diffusion

speed of water molecules in the direction perpendicular to and along the nerve fiber bundle, respectively. By comparing the RD and AD values, the directionality and homogeneity of the diffusion of water molecules in the tissue can be understood. Using diffusion tensor imaging to study white and grey matter alterations in monkey brain after ischaemic stroke, the MD, RD and AD of white matter were significantly decreased during hyperacute stroke, and staining revealed that white matter was slightly damaged at 8 hours post-stroke, and severely damaged at 48 and 96 hours post-stroke.²²

Treatments of WMI in Ischaemic Stroke

Most of the treatments for WMI after ischaemic stroke have been initiated in terms of reducing neuroinflammation, restoring circulatory blood flow to the brain. In recent years, with the deepening of understanding and emphasis on WMI, more and more research directions have been identified. In a study that utilised aged female ischaemic mouse model was found to attenuate WMI and promote long-term functional recovery.²³ From the perspective of promoting neurogenesis and proliferation of endogenous neural stem/progenitor cells, artesunate (a water-soluble derivative of artemisinin with anti-malarial, immunomodulatory and anti-inflammatory properties) ameliorated ischaemia-reperfusion injury and attenuated WMI.²⁴ With the attention and emphasis on WMI, future research on WMI in ischemic stroke will be more indepth to improve WMI after stroke at an early date, improve neurological function, reduce the disability rate, and reduce the national healthcare burden.

White Matter Injury and Intracerebral Hemorrhage

Characteristics and Mechanisms of Injury in WMI After Intracerebral Haemorrhage

Intracerebral hemorrhage (ICH) is a non-traumatic bleeding caused by rupture of blood vessels in the brain parenchyma and accounts for 10–15% of all stroke cases²⁵ Since 50–70% of ICH mostly occurs in the basal ganglia region, it is prone to disability and even death.²⁶ This is due to the fact that the internal capsule of the basal ganglia is a white matter plate composed of upward and downward fibers linking the cerebral cortex to the brainstem and spinal cord. The region of the internal capsule of the basal ganglia contains a large number of white matter fibres, making it susceptible to direct pressure from the haematoma and secondary damage from blood toxicity products, leading to hemiparesis (partial corticospinal tract and cortical damage), hemianopsia (central visual radiation damage), sensory deficits (central thalamic radiation damage) and other sequelae.

There are numerous mechanisms of WMI injury after cerebral haemorrhage, including direct compression and pneumatic pressure injuries caused by haematoma, haemodynamic changes, cerebral oedema, disruption of the blood-brain barrier, effects of erythrocyte catabolic products, excitotoxic effects, oxidative stress, neuroinflammation, and apoptosis.^{27,28} Due to prolonged ischemia of the cerebral white matter, resulting in demyelinating lesions of the white matter, which are manifested as high signals in the cerebral white matter on MRI. MRI has shown that the volume of WM high-signal is higher after ICH than after ischemic stroke. It has also been shown that WMI is present in more than 77% of ICH patients, and that axonal damage occurs in subcortical white matter regions after haemorrhage.²⁹ Electron microscopy revealed abnormalities of myelin sheaths, axonal membranes, mitochondria and axonal cytoskeleton, including structural disorganisation and lysis of myelin sheaths.^{30,31} The number of microtubules is reduced or completely lost, the spacing of neurofilaments is reduced, dense clustering occurs, axonal membrane segments are separated from the inner layer of the myelin sheath, axonal and myelin spaces are enlarged, and mitochondria are swollen.⁸ A recent study showed that DTI predicts functional outcome 6 months after acute ICH and that mean white matter diffusion rate correlates with poor outcome.³² In animal experiments, it was noted that on day 1 after ICH, a large amount of degraded Myelin basic protein (dMBP) was seen in the core and margins of the haematoma, and the white matter bundles were morphologically normal; by day 3 after ICH, the dMBP staining was lighter, and the white matter bundles were fragmented; and on day 28 after ICH, no dMBP was detected in the ipsilateral striatum of the experimental animals. dMBP was not detected even inside the lesion or at the lesion margin.³³

Treatments of WMI in Intracerebral Haemorrhage

The treatment of WMI after ICH is mostly based on reducing neuroinflammation and oxidative stress, removing oedema and haematoma, improving the microenvironment of the brain, stem cell transplantation, and microRNA therapy.²⁶ Gao et al³⁴ investigated that by regulating microglial cells/macrophages, they were able to accelerate haematoma clearance after ICH and improve secondary WMI. Li J et al³⁵ found that oxidised picloram ameliorated ICH-induced WMI and neurological deficits by modulating the gut microbiota. Besides, oligodendrocytes and axonal plasticity play important roles in maintaining the structure and function of white matter. It has been demonstrated that electroacupuncture promotes myelin regeneration and alleviates cognitive deficits by promoting oligodendrocyte precursor cell differentiation in a rat model of subarachnoid haemorrhage.³⁶ Thus, interventions targeting oligodendrogliogenesis and axonal plasticity may improve functional outcomes after ICH.

This demonstrates the critical role of white matter in neurological recovery after stroke. Without protection of white matter and its fibres, true and lasting neuroprotection cannot be achieved. Protecting the integrity and connectivity of white matter can facilitate the rehabilitation of axonal networks and improve stroke prognosis.

White Matter Injury and Alzheimer's Disease

Characteristics and Mechanisms of WMI in Alzheimer's Disease

Alzheimer's disease (AD) is an age-related neurodegenerative disease. Previous research on AD has focused on the A β theory and the Tau protein theory, and it is widely believed that AD WMI is the result of grey matter disease and neuronal death. However, attention has only been drawn to the study of brain WMI in AD after an MRI study noted that WMI preceded amyloid plaques and neuroprogenitor fibril tangles in early-onset familial AD in humans, late-onset AD in humans, and rodent models of AD.^{37,38}

There are numerous mechanisms of AD related WMI damage including: ageing, $A\beta$, inflammatory response, oxidative stress, cholesterol, familial AD genes, excitotoxicity, DNA damage and others.

These are important contributors to WMI. Loss of myelin and decreased levels of MBP may lead to accelerated deposition of A β , resulting in increased deposition of A β plaques in the brains of AD patients. MBP, an intracellular protein and a major structural protein component of myelin, has been shown to bind A β and inhibit the formation of A β protofibrils in AD, which regulates A β in the extracellular space of the brain in AD patients. Meanwhile, A β itself is toxic to OPCs and inhibits myelin formation,³⁹ which also contributes to WMI.

Studies have shown that myelin and oligodendrocyte damage precedes the appearance of amyloid plaques and neuroprogenitor fibre tangles in early-onset AD and sporadic late-onset AD. Analysis of postmortem brain tissue from patients with AD showed chemical alterations of the white matter: significantly lower levels of total proteins, MBP, myelin, cyclic nucleotide phosphohydrolase, and cholesterol, as compared to patients without dementia.⁴⁰ Hoy⁴¹ performed DTI in a preclinical AD population and found abnormalities in DTI. The same DTI study by Maier-Hein found significant and extensive white matter degenerative damage prior to the onset of dementia.⁴² A meta-analysis of voxel-based morphometry in AD patients and healthy individuals showed reduced white matter volume in AD subjects.³⁷ Compared to patients with mild cognitive impairment, AD patients had reduced anisotropy value scores in frontal white matter, corpus callosum white matter, fornix and hippocampus, cingulate gyrus and fasciculus, unicervical and superior longitudinal fasciculus, and subfrontal occipital and inferior longitudinal fasciculus.⁴³ In experimental animal models, the 3 XTg-AD mouse model had myelin loss and OPCS loss at both 6 and 12 months of age, and even the surviving OPCS had functional abnormalities and impaired myelin repair.⁴⁴ APP/PS1 are double transgenic mice expressing a chimeric mouse/human amyloid precursor protein and a mutant human presenilin 1, in the CNS neurons. In APP PS1 transgenic mice, reduced fibre bundle volume, axonal loss and myelin breakdown were also shown in the corpus callosum and anterior connectivity.⁴⁵ All of the above indications suggest that WMI occurs in the AD brain.

Treatments of WMI in Alzheimer's Disease

Aerobic exercise is an effective preventive and therapeutic modality for AD, and exercise improves AD brain WMI. Running reduces the loss of myelin fibres in the hippocampus in the APP/PS1 mouse model of AD.^{46,47} Exercise prior to

the onset of AD pathology prevented memory loss and loss of myelin in the white matter in the APP/PS1 mouse model of AD.⁴⁸ In addition to this, traditional Chinese medicines have also made important contributions in attenuating AD WMI. Gardenia jasminoides J. Ellis extract attenuates white matter damage by inhibiting neuroinflammation to promote the differentiation of oligodendrocyte precursor cells.⁴⁹ Shenzhiling oral solution plays its therapeutic role in AD by promoting the oligodendrocyte PI3K/Akt-mTOR Shenzhiling oral solution exerts its therapeutic effect on AD by promoting the PI3K/Akt-mTOR signalling pathway in oligodendrocytes.⁵⁰

White Matter Injury and Multiple Sclerosis

Characteristics and Mechanisms of WMI in Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system that results in large focal lesions in the white matter of the brain and spinal cord, characterised by primary demyelination with varying degrees of axonal loss, with motor and cognitive deficits progressing over time.⁵¹

MS is characterised by focal lesions, with large areas of the brain remaining unaffected. However, it is well known that microglia activation, axonal pathology, and myelin reduction are present in areas of what is known as normal white matter, which is thought to underlie a number of neurological deficits.⁵² MS white matter pathology can be divided into three morphological patterns. The first pattern represents the typical demyelinating plaque, which is characterised by almost complete demyelination with varying degrees of axonal retention and axonal swelling. The second pattern, characterised by demyelinating lesions contains varying numbers of myelinated axons with a small number of demyelinated axons and varying amounts of axonal swelling. The myelinated axons range from scattered fibres to strips of varying thickness and the demyelination is a mixture of primary and secondary demyelination. A third pattern, characterised by reduced myelin staining and a large number of apoptotic nuclei is well defined. Axonal staining shows fragmentation of many axons with reduced myelin staining but no clearly demyelinated axons.⁵³

White matter tract damage in MS has been found to be associated with iron deposition in deep grey matter, with increased iron levels in the right and left caudate nucleus as well as in the left thalamus in MS patients, and MS patients presenting with reduced DTI-derived measures of tissue integrity in the associated white matter tracts.⁵⁴ g-ratio, the ratio of the inner diameter (axons plus myelin) of a myelinated axon (axons plus myelin) to the outer diameter, is related to conduction speed, with thicker axons and thicker myelin sheaths will produce faster electrochemical information conduction.⁵⁵ The first study to examine and report changes in brain g-ratio in MS patients found that the average g-ratio of white matter in peripheral plaques was higher than that of normal white matter in MS patients, and that myelin sheaths in myelinated plaques were thinner, even after partial regeneration of the myelin sheaths.⁵⁶

Treatments of WMI in Multiple Sclerosis

Limited interventions with clinically used pharmacologically active compounds such as interferon- β , mitoxantrone, fingolimod and monoclonal antibodies are mainly associated with adverse drug reactions.⁵⁷ Despite extensive research on neuroprotective treatments for multiple sclerosis, a number of complications remain. The available medications only relieve symptoms but do not stop disease progression. Constraint-induced movement therapy, a physical movement rehabilitation therapy, has been observed in the contralateral corpus callosum, ipsilateral supraoccipital gyrus, ipsilateral superior temporal gyrus, and contralateral corticospinal tracts, where improvement in white matter integrity has been observed.⁵⁸

Animal models with the gliotoxin ethidium bromide mimic the behavioural and neurochemical alterations seen in multiple sclerosis. Dysregulation of AC/cAMP/CREB signalling is involved in the progression of MS, including mitochondrial dysfunction, reduction in nerve growth factor, neuronal inflammation, apoptosis, and white matter degeneration. Forskolin medication followed by treatment of the disease improved myelin regeneration through enhancement of myelin basic proteins and an increase in AC in brain homogenate, cAMP and CREB levels to improve myelin regeneration as well as reduce oligodendrocyte death.⁵⁹ Folate-aminopterin constructs were well tolerated and attenuated inflammation and lesion development in a rat model of chronic progressive MS.⁶⁰ microRNAs are increasingly recognised as key regulators of glial development. miR-125a-3p was found to be a new player in oligodendrocyte

physiology, regulating the differentiation of OPCs in vitro. miR-125a-3p lentiviral overexpression impaired OPC maturation, whereas inhibition of miR-125a-3p expression accelerated myelin regeneration.⁶¹ During demyelination, inhibition of miR-146a reduced the inflammatory response, demyelination, axon loss, the number of infiltrating macro-phages, and increased the number of myelinating oligodendrocytes.⁶²

Currently, there are limited studies on WMI after MS, and it is difficult to find an animal model of MS that perfectly mimics the pathogenesis and pathological features of human MS. Starting from oligodendrocytes should be a good entry point, and it is believed that more effective treatments will be discovered later.

In summary, white matter plays a crucial role in for the CNS to maintain normal function, and myelin regeneration is the only known ability of the CNS to self-repair, potentially providing complete anatomical and functional neural regeneration. The discovery of oligodendrocyte precursor cells in the 1980s and the discovery of visualization and imaging techniques have led to a heightened interest in the role of white matter.⁶³ oPCs are oligodendrocyte precursors responsible for myelin development during embryogenesis, renewal, and repair of the mature CNS. oPCs are responsible for the repair of myelin sheaths and the remyelination of axons, which indirectly contributes to neuroprotection, and regeneration of myelin sheaths is critical to prevent neurodegeneration.

This article summarizes the current status of WMI after ischemic stroke, cerebral hemorrhage, Alzheimer's disease, multiple sclerosis, and other CNS diseases, as well as the pathogenesis and current therapeutic approaches. Significant advances have been made in the study of molecular mechanisms targeting the CNS WMI, including ischemia and hypoxia, the occupancy effect of perihematoma edema, blood-brain barrier impairment, toxicity of different biochemical metabolites, glutamate-mediated neurotoxicity, neuroinflammatory response, and oxidative stress.

Although scholars have proposed different treatments for different mechanisms in animal model groups, it is uncertain which treatments can be applied to clinical treatments, even though some of the treatments applied in the clinic are not yet widely available as well as being used on a large scale. With the emphasis on WMI, it is believed that more and more in-depth and thorough studies will be conducted to seek new intervention targets to better serve clinical care in CNS diseases.

Disclosure

The authors report no conflicts of interest in this work.

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