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REVIEW

Stroke with White Matter Lesions: Potential Pathophysiology and Therapeutic Targets

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Abstract

Stroke is one of the most common causes of morbidity and mortality among adults globally. Significant advancements have been made in elucidating its pathophysiology, with stroke categorized into pathological subtypes, such as ischemic stroke (IS) and hemorrhagic stroke. White matter lesions (WMLs) identified on magnetic resonance imaging rank as a hallmark of cerebral small vessel disease and are associated with vascular risk factors. They are linked to adverse outcomes like dementia, depression, and an increased risk of both first-ever and recurrent strokes, independent of other risk factors. Despite the evidence indicating the close link between WMLs and stroke, their underlying pathophysiological relationship remains unclear. This study aims to provide an overview of the current knowledge and recent advances in epidemiology, risk factors, and pathophysiological mechanisms of WMLs and stroke, focusing on their interconnection and emerging therapeutic targets.

Key words: stroke; leukoencephalopathies; pathophysiology; therapeutic targets

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Introduction

White matter lesions (WMLs), also known as leukoaraiosis (LA), are commonly detected on magnetic resonance imaging (MRI) using approaches like fluid-attenuated inversion recovery (FLAIR) imaging (You et al, 2018; Yuan et al, 2021). WMLs serve as an independent risk factor for stroke ranging in the prevalence from 4% to 44% on computed tomography reaching up to 100% on MRI (Ederle et al, 2013; Hokkanen et al, 2013). However, its prevalence increases significantly with age, from approximately 10% in younger individuals to over 70% in older individuals aged 80–89 years (Graff-Radford et al, 2020). Moreover, stroke itself can lead to WMLs; for instance, 15–25% of strokes are subcortical white matter stroke (WMS) associated with WMLs (Nägele et al, 2024). Despite the strong association between stroke and WMLs, their underlying pathological mechanism remains poorly understood.

This study aims to review the pathophysiology and clinical significance of WMLs in the context of stroke, an emphasizing their underlying mechanisms. It

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also discusses treatment strategies for WMLs and stroke, provides recommendations for clinical practice, and underscores future research directions. Furthermore, this study proposes conceptual insights into the potential mechanisms associating WMLs to stroke.

Epidemiology of Stroke and WMLs

Epidemiology of Stroke

Stroke is the second leading cause of mortality among individuals over 60 years of age, according to the World Health Organization (Feigin et al, 2023; Murray and Lopez, 1996). However, stroke epidemiology varies across countries and ethnicities and has been changing rapidly (Bhutta et al, 2022; El-Hajj et al, 2016; Han et al, 2018; Venketasubramanian, 2021). In 2021, there were 11.9 million new stroke cases worldwide, with 13.8 million stroke survivors (GBD 2019 Stroke Collaborators, 2021; GBD 2021 Diabetes Collaborators, 2023). Global Burden of Disease study ranks stroke as the third most common cause of disability-adjusted life-years globally (GBD 2021 Diabetes Collaborators, 2023). Each year, approximately 7.08 million people die from stroke globally, with ischemic stroke (IS) causing 3.48 million deaths, hemorrhagic stroke (HS) 3.25 million and subarachnoid hemorrhage (SAH) 0.35 million (GBD 2016 Neurology Collaborators, 2019; Tsao et al, 2022). However, stroke represents approximately 10.7% of global mortality (GBD 2021 Diabetes Collaborators, 2023; Strong et al, 2007).

This article also reviewed the epidemiology of stroke based on age, sex, ethnicity, region, and country. Age is the strongest risk factor, with the incidence of stroke doubling each decade after age 55 (Scott et al, 2022). Sex differences are also evident: men exhibit a higher incidence of stroke at younger ages, while women, who generally live longer, face a more significant stroke burden in older age groups (Norman et al, 2022; Yu et al, 2023). Ethnic and regional disparities further underscore the complexity of stroke epidemiology. For example, individuals of African or South Asian ancestry have higher stroke rates than those of European descent, largely due to differences in the elevated prevalence of hypertension and diabetes (Patel et al, 2021). Geographic variations reveal that over 80% of global stroke mortality occurs in low and middle-income countries, driven by disparities in healthcare access, preventive strategies, and lifestyle factors (Aguirre et al, 2023; Markus, 2022).

These demographic and regional patterns highlight stroke as a heterogeneous disease impacted by diverse, interconnected factors, providing valuable context for understanding prevention and treatment approaches.

Epidemiology of WMLs

There are limited epidemiological studies on WMLs, and no consensus on their prevalence, morbidity, and mortality has been reached. A hospital-based cross-sectional study in China involving 4683 hospitalized WML patients revealed that their incidence increases with age, with older women, particularly those over 60, being more susceptible than men (Lin et al, 2017). The loss of estrogen may play

a crucial role in this gender disparity (Rastogi et al, 2021; Seo et al, 2013). In Finland, a study assessing the radiologic features of silent brain infarcts and WMLs in 669 patients employed logistic regression to identify predisposing factors for both conditions. The findings uncovered that WMLs are not uncommon among young stroke patients (Putaala et al, 2009). In the United States, studies have revealed that Hispanics and African-Americans tend to have relatively larger brain volumes and a heavier burden of WMLs compared to Whites, with vascular diseases contributing to these racial/ethnic differences in WML severity (Morrison et al, 2023; Royse et al, 2024). Turney et al (2023) reported a strong association between age and WML volume and observed that brain aging was more pronounced in Latinx and White adults, in late life than in midlife. Conversely, Black adults exhibited an accelerated pattern of brain aging beginning in midlife. Additionally, non-Hispanic Black older adults may face a higher risk of dementia due to racial discrimination, and everyday experiences of racial discrimination have been associated with a faster accumulation of WML over time (Zahodne et al, 2023). Furthermore, a study evaluating the prevalence and risk factors of WMLs among Tibetans revealed similar risk factors for those living at high altitudes and those living in the plains (Jin et al, 2020). However, they suggested further research to validate these findings. The aforementioned studies collectively indicate that WMLs affecting a significant portion of the population, with outcomes impacted by various factors, including age, sex, ethnicity, and social region. These observations highlight the significance of further investigations to provide valuable insights into WMLs and their associated risk factors.

WMLs and Risk Factors for Stroke

Risk Factors for Stroke

A standardized international case-control study identified 10 potentially modifiable risk factors for stroke, including a history of hypertension, current smoking, waist-to-hip ratio, diet risk score, regular physical activity, diabetes mellitus, alcohol intake, psychosocial stress and depression, cardiac causes, and the apolipoprotein (Apo) B/Apo A1 ratio (Fig. 1) (O'Donnell et al, 2016). The combined population-attributable risk for all strokes was 87.1% (82.2–90.8) (Hankey, 2020). These are among the most commonly observed risk factors for stroke. However, as the disease progresses, additional risk factors warrant further investigation. WMLs have been reported as an independent risk factor for stroke, associated with an increased risk of both first and recurrent stroke, along with an elevated risk of stroke recurrence (Wang et al, 2022). Furthermore, the global outbreak of COVID-19 has introduced a novel risk factor for stroke, attributed to its potential inflammatory and prothrombotic effects, eventually leading to IS (Sagris et al, 2021).

WMLs as an Independent Risk Factor for Stroke

WMLs are prevalent in patients with both HS and IS (D'Anna et al, 2021). They are an independent risk factor for stroke and are linked to increased risk of stroke, dementia, and mortality (Rosbergen et al, 2023). A study found that patients

with a history of intracerebral hemorrhage (ICH) and advanced WMLs had a significantly higher risk of IS (adjusted hazard ratio (HR) 2.62, 95% CI 1.22–5.60) and HS (HR 33.96, 95% CI 1.52–760.95) compared to those with mild WMLs. During a mean follow-up of 1.9 years, the incidence of IS was highest in the advanced WML group at 8.1 per 100 person-years, while the hemorrhagic stroke rate was 2.1 in this group (Park et al, 2021). Similarly, a meta-analysis including 10,584 ICH patients found that moderate-to-severe WMLs significantly increased the odds of poor functional outcomes (OR 1.805, 95% CI 1.320–2.469) and all-cause mortality (OR 3.27, 95% CI 2.07–5.18), with worsening WML severity linking with poorer outcomes (You et al, 2022).

These observations present WMLs as valuable prognostic biomarkers and diagnostic indicators for stroke. When WMLs are detected through imaging, the associated stroke risk should be considered, and detailed screening should be conducted promptly.

The Status of WMLs in the Prognosis of Stroke

WMLs significantly affect the prognosis of stroke patients (Huo et al, 2021). Moderate-to-severe white matter WMLs are associated with poor prognosis impacting functional independence, neuroprognostication, and recanalization efficiency. In patients with large vessel occlusion (LVO) stroke, WML has been found to be closely linked to 90-day functional outcomes with increasing WML volume (0 to 4 mL) (Griessenauer et al, 2020). WML severity has also been associated with worse 90-day modified Rankin Scale scores in patients undergoing endovascular treatment (Benson et al, 2021; Guo et al, 2019; Mikati et al, 2020; Regenhardt et al, 2021). The modified Rankin Scale score, widely used as an indicator of postoperative outcome, remains relatively subjective; therefore, implementing a more objective scoring system with the greater predictive value could enhance outcome assessments (Benson et al, 2021). A clinical study by Shi et al (2012), evaluating 105 patients with moderate-to-severe WMLs in the deep white matter (DWM), showed that WMLs were correlated with hemorrhagic transformation after mechanical thrombectomy and an increased risk of parenchymal hematoma. Similarly, moderate-to-severe WMLs have been associated with poor outcomes in patients with successful recanalization for IS involving anterior LVOs (Liu et al, 2019). Compared to overt stroke lesions, concomitant silent lesions, such as WMLs and covert lacunar infarcts, substantially impact post-stroke cognitive and motor outcomes (Valdés Hernández et al, 2021). Regarding stroke recurrence, a study by Andersen et al (2017) investigating the predictors of recurrent IS in 832 patients without atrial fibrillation identified that WMLs was an independent predictor of recurrent IS.

In ICH, patients typically present with interdependent WMLs. A prospective cohort study in patients with acute ICH demonstrated an association between WML severity and both the occurrence and intraventricular extension of hemorrhage (Mistry et al, 2020). Furthermore, a meta-analysis of nine studies including 4948 patients, revealed a significant association between WHLs and worse functional outcomes, with higher mortality in ICH patients (Yu et al, 2019). Although WMLs

have been recognized as an independent predictor of poor neurological and functional outcomes as well as associated with ICH volume, their severity does not correlate with hematoma size or growth (Hansen et al, 2020; Vagal et al, 2020). However, WMLs are a risk factor for intraventricular hemorrhage and independently increase the risk of ventricular rupture (Vagal et al, 2020). Despite these observations, the precise relationship between HS and WMLs remains unclear, warranting further investigations. The severity of WMLs is linked to stroke prognosis. Endothelial dysfunction has been suggested as a contributing factor to increased WML volume, potentially explain the relationship between WML volume and poor stroke outcomes (Liu et al, 2021a; Toya et al, 2021).

From an imaging perspective, WMLs are typically detected as hyperintensities on T2-weighted or FLAIR MRI. However, WML volume and regional distribution are associated with varying risk levels. For instance, periventricular WMLs are more strongly correlated with stroke recurrence than deep WMLs due to their proximity to major vascular structures (Khademi et al, 2021). Advanced imaging approaches including diffusion tensor imaging (DTI) and quantitative susceptibility mapping offer deeper insights into microstructural changes and vascular integrity, enabling more precise risk assessments.

Beside imaging, biomarkers have emerged as promising tools for improving risk stratification. Higher plasma neurofilament light chain (NFL) levels, a marker of axonal damage, have been correlated with WML burden and stroke outcomes (Qu et al, 2021). Similarly, inflammatory markers like interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) have been reported as predictors of WML progression and elevated stroke risk (Zhang et al, 2022a). Integrating the biomarker analysis with imaging findings may enhance early diagnosis and support personalized treatment strategies.

These combined approaches underscore the significance of advanced imaging techniques and biomarker assessment in enhancing the predictive accuracy and clinical management of WMLs.

Pathology and Definition of WMLs and Stroke

Pathophysiology of Stroke

Pathophysiology of IS

IS occurs due to arterial occlusion, resulting in disrupted cerebral blood flow and subsequent neurological deficits. Its primary causes include atherosclerosis, thrombosis, and embolism. Atherosclerosis involves lipid deposition on arterial walls, triggering vascular inflammation and thrombosis. Emboli, usually originating from distant sites such as the heart, are common in cardioembolic strokes and strongly associated with atrial fibrillation. Elevated levels of circulating inflammatory markers, such as C-reactive protein (CRP) and IL-6, are significantly associated with risk of atherosclerosis-related strokes, demonstrating the systemic inflammatory contribution to IS pathology (Coveney et al, 2022; McCabe et al, 2023).

At the cellular level, ischemia triggers excitotoxicity, oxidative stress, and neuroinflammation, which are central to IS pathology (Fig. 2). Excitotoxicity is caused

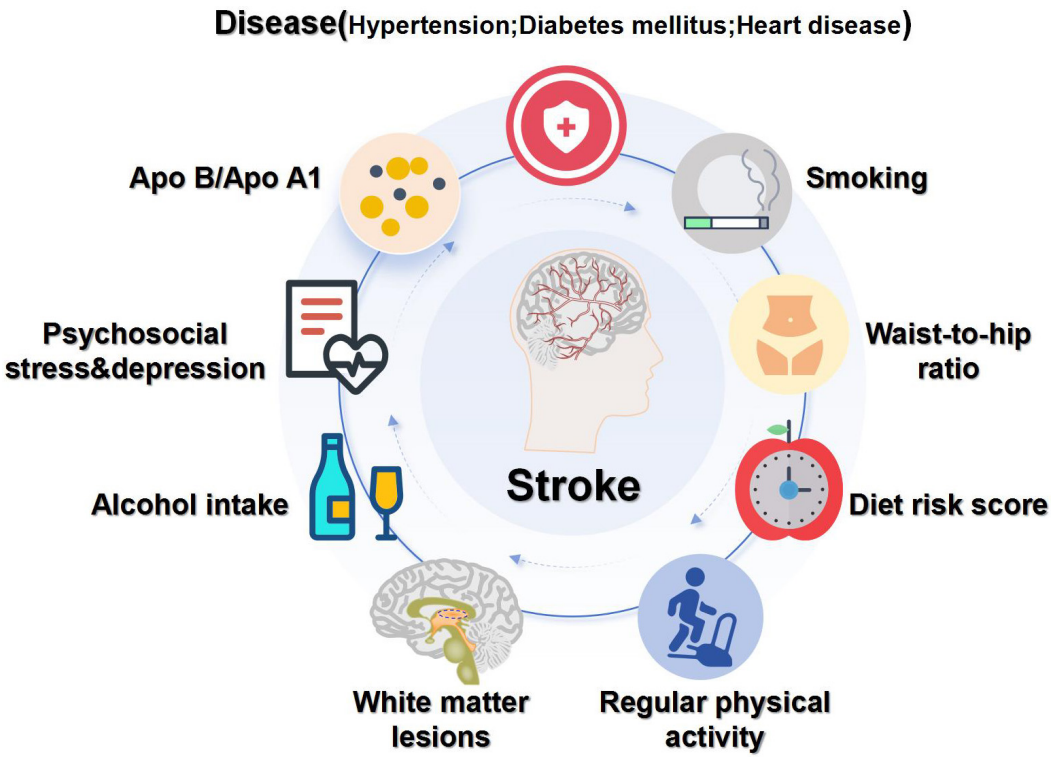

Fig. 1. Stroke-associated risk factors. This figure was developed using Adobe Illustrator 22.1 (Adobe Systems Incorporated, San Jose, CA, USA). Apo, apolipoprotein.

by ATP depletion, which disrupts ionic homeostasis and causes excessive calcium influx and glutamate release. Persistent calcium influx leads to mitochondrial dysfunction and neuronal death (Belov Kirdajova et al, 2020). Clinically, elevated extracellular glutamate levels have been observed in acute IS patients, which are associated with worse functional outcomes, suggesting glutamate excitotoxicity a crucial therapeutic target (Gill, 2022).

Oxidative stress further exacerbates ischemic injury by generating reactive oxygen species (ROS), which damage cellular structures and compromise the blood-brain barrier (BBB). ROS also amplifies neuroinflammation, activating microglia and promoting the release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (Jayaraj et al, 2019). Elevated oxidative stress markers, such as serum malondialdehyde (MDA) levels, correlate with worse outcomes including larger infarct volumes and higher mortality rates among IS patients (Elhamrawy et al, 2023).

Neuroinflammation plays a dual role in IS, contributing to both acute damage and delayed repair processes (Shi et al, 2019). Positron emission tomography (PET) imaging studies using microglial activation tracers have demonstrated elevated neuroinflammatory activity in peri-infarct regions within hours of stroke onset, directly linking inflammation to the progression of ischemic injury (Barca et al, 2022; Zhang et al, 2021).

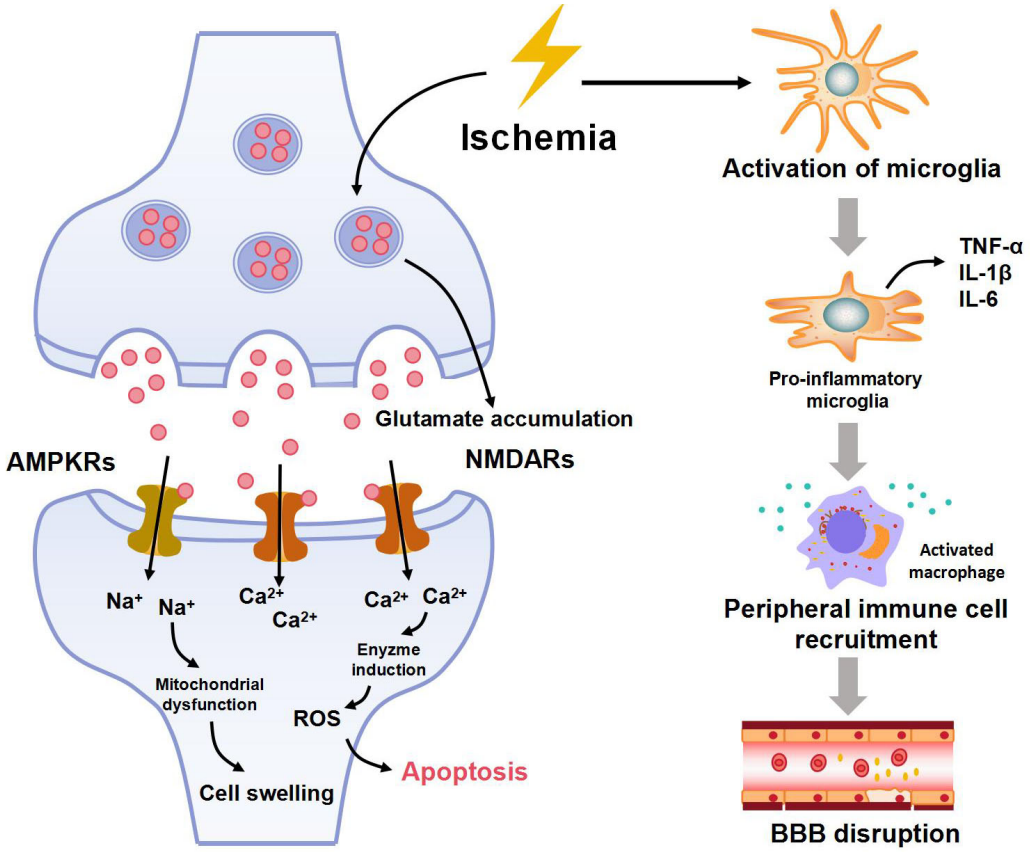

Fig. 2. Pathophysiology of stroke. The figure was created using Adobe Illustrator 22.1. ROS, reactive oxygen species; AMPKRs, AMP-activated protein kinase receptors; NMDARs, N-methyl-D-aspartate receptors; BBB, blood-brain barrier; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6.

Pathophysiology of Hemorrhagic Stroke

Hemorrhagic stroke (HS), including ICH and subarachnoid hemorrhage (SAH), occurs due to the rupture of cerebral blood vessels, usually caused by hypertension, anticoagulant use, or cerebral aneurysms. In ICH, the extravasated blood forms a hematoma that compresses adjacent brain tissue, inducing secondary injuries such as cytotoxicity, oxidative stress, and inflammation. Hemoglobin and its breakdown products, such as heme and iron, exacerbate neuronal damage and disrupt BBB by generating ROS. Higher levels of non-transferrin-bound iron (NTBI) in cerebrospinal fluid have been linked to increased perihematomal edema and worse functional outcomes, highlighting the role of iron-induced toxicity in ICH patients (Liu et al, 2020; Ramadhan et al, 2023).

Inflammation further aggravates the damage, as microglia rapidly release pro-inflammatory cytokines and chemokines after ICH onset (Zille et al, 2022). These inflammatory mediators recruit peripheral immune cells, leading to additional BBB disruption and leukocyte infiltration. Post-mortem analyses of ICH patients have demonstrated increased neutrophils and monocyte infiltration in perihematomal regions, which correlates with larger hematoma volumes and reduced survival rates (Mackey et al, 2021). However, during the recovery phase, microglia-mediated

phagocytosis plays a crucial role in clearing cellular debris and promoting tissue repair. This dual role of inflammation highlights the complexity of HS pathology and underscores the challenges in developing targeted therapies.

Pathophysiology of WMLs

Neurovascular Unit Dysfunction

The neurovascular unit (NVU), comprising endothelial cells, astrocytes, pericytes, neurons, and extracellular matrix components, plays a critical role in maintaining cerebral homeostasis by regulating neurovascular coupling and cerebral blood flow. Pathological changes in the NVU, such as impaired neurovascular signaling and reduced vascular reactivity, are closely linked to WMLs. These changes usually arise from processes such as large-artery stenosis (LAS), cerebral small vessel disease (CSVD), and oligodendrocyte dysfunction (Manukjan et al, 2020; Takahashi, 2022). Together, they contribute to chronic hypoperfusion and neuroinflammation, exacerbating white matter damage and increasing stroke susceptibility. Fig. 3 illustrates these interconnected processes, highlighting the roles of NVU dysfunction, BBB disruption, and inflammation in driving white matter damage. The identification of NVU dysfunction and glymphatic system impairment as key mechanisms offers valuable insights for early detection and risk stratification. Advanced imaging modalities, including DTI and dynamic contrast-enhanced MRI, have emerged as promising tools to identify subtle white matter changes and monitor disease progression. These techniques align with recent studies underscoring their potential to detect microstructural white matter damage before clinical symptoms become evident (Yang et al, 2024).

Large-artery stenosis (LAS), defined as $\geq$50% narrowing of intracranial or extracranial arteries, is closely associated with disrupted cerebral blood flow and hypoperfusion, driving WML progression. A longitudinal study on intracranial LAS patients demonstrated that severe intracranial arterial stenosis significantly increased the risk of WML progression, particularly in periventricular areas, with a 2.8-fold and 3.0-fold higher risk for grade 2 and grade 3 stenosis, respectively (OR 2.8, 95% CI 1.4–5.5; OR 3.0, 95% CI 1.2–7.3) (Zhong et al, 2022). Intracranial LAS worsens WML severity regardless of the number of obstructions, while extracranial LAS, especially in the external carotid artery, disrupts cerebral blood flow regulation, further intensifying hypoperfusion. Cerebrovascular reactivity (CVR), a key indicator of vascular responsiveness, is often impaired in LAS, contributing to WML progression in hypoperfused regions. Bahrani et al (2021) introduced a novel method to assess dynamic WML changes, indicating that reduced CVR was associated with a 15% higher WML growth rate, particularly in patients with cognitive decline.

Cerebral small vessel disease (CSVD), which involves pathological changes in small arteries, arterioles, and capillaries, is another major contributor to WMLs. Arteriolosclerosis, characterized by vascular wall necrosis and lipid deposition, causes stenosis and hemodynamic changes, resulting in chronic ischemia and white matter damage (Shindo et al, 2020). According to the Rotterdam Study, individuals with severe CSVD had a 2.5-fold increased risk of IS and a 3.2-fold higher risk of cogni-

tive decline compared to those with minimal CSVD changes (Vermeer et al, 2007). BBB disruption is a hallmark of CSVD, allowing the infiltration of plasma proteins and immune cells into the white matter. The BBB, formed by endothelial cells, tight junction proteins, pericytes, and astrocytic endfeet, which maintain brain homeostasis by regulating molecular transport. Its dysfunction leads to the extravasation of toxic substances and pro-inflammatory mediators, aggravating neuroinflammation, promoting oxidative stress, and accelerating demyelination, ultimately resulting in white matter damage (Sun et al, 2021; Takata et al, 2021).

Vascular remodeling, characterized by vascular smooth muscle cell proliferation and intimal thickening, is another key mechanism contributing to WMLs. Chronic ischemia triggers remodeling, reducing vascular compliance and impairing microvascular perfusion, exacerbating white matter injury. Research has revealed significant arteriolar wall thickening and luminal narrowing in brain regions affected by severe WMLs (Liu et al, 2024).

Oligodendrocyte dysfunction further intensifies NVU impairment in WMLs. Oligodendrocytes and their precursor cells (OPCs) are essential for maintaining and repairing myelin. NVU dysfunction disrupts the microenvironment required for OPC proliferation and differentiation, limiting myelin regeneration and exacerbating white matter damage (Lorenzini et al, 2020).

Glymphatic System Dysfunction

The glymphatic system, a cerebrospinal fluid (CSF)-based clearance pathway, is pivotal in maintaining brain homeostasis by facilitating the removal of metabolic waste (Tian et al, 2022). Dysfunction of this system is associated with the pathogenesis of WMLs, particularly through mechanisms involving venous collagenosis (VC) and venous hemodynamic abnormalities (Sabayan and Westendorp, 2021).

VC, characterized by collagen thickening in periventricular venous walls, has a strong correlation with WMLs severity. Patients with venous dysfunction exhibit WML volume of 25%–30% higher than those in healthy individuals (Kapadia and Dmytriw, 2021). Increased venous pressure caused by VC impairs the clearance of metabolic waste, exacerbating glymphatic dysfunction and promoting white matter damage. Hypertension further exacerbates VC by increasing venous wall stress and enhancing collagen deposition.

Venous hemodynamic abnormalities, such as jugular venous reflux (JVR) and dural arteriovenous fistula (DAVF), also disrupt glymphatic function. JVR triggers retrograde venous flow and hypertension, impairing CSF drainage and subsequent white matter injury (Toledano-Massiah et al, 2020). Similarly, DAVF induces severe venous hypertension through arterial shunting, worsening hypoperfusion, and BBB damage (Xie et al, 2023). Chronic venous hypertension caused by these conditions restricts venous outflow, aggravating WML progression through ischemia, edema, and oxidative stress.

Pathological Relationship between Stroke and White Matter Damage

As discussed earlier, WMLs are intricately linked to stroke. The damage to white matter impairs neurovascular and glymphatic dysfunction, resulting in changes

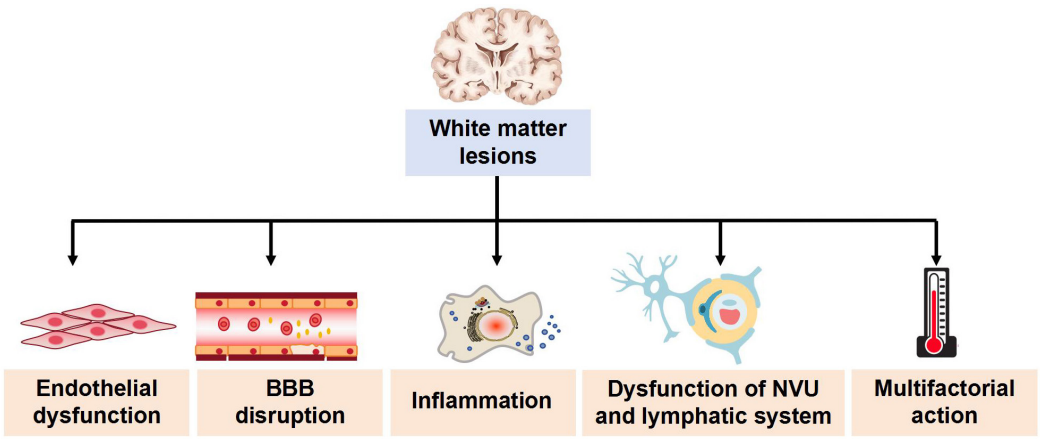

Fig. 3. Hypothetical pathogenesis of white matter lesions. The figure was generated through Adobe Illustrator 22.1. BBB, blood-brain barrier; NVU, neurovascular unit.

in cerebral hemodynamics and alterations in arterial and venous blood vessels (Fig. 4). This makes the white matter more susceptible to ischemia and bleeding, thereby increasing the risk of recurrent strokes. A cohort study involving over 1800 patients demonstrated that moderate-to-severe WMLs independently increased the risk of recurrent stroke by 67% (95% CI 1.39–2.01), regardless of traditional risk factors such as hypertension and diabetes (Uniken Venema et al, 2021).

Stroke further aggravates white matter damage through pathological events such as excitotoxicity, oxidative stress, and neuroinflammation. White matter comprises astrocytes, neuronal axons, and oligodendrocytes (myelin sheath), which are vulnerable to cell swelling and tissue edema after stroke (Lo et al, 2003). Stroke induces activation of multiple proteases, such as calpains and matrix metalloproteinases, degrades key structure of white matter like neurofilaments and myelin-basic proteins, resulting in axonal disruption and demyelination.

Furthermore, the ionic imbalance caused by stroke leads to extracellular glutamate accumulation. Overactivation of oligodendrocyte receptors, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA), results in excessive Ca^{2+} and Na^{+} influx, causing oligodendrocyte death (Káradóttir et al, 2005; Sánchez-Gómez et al, 2003). Clinical evidence indicates that stroke patients with high WML burden experience larger infarct volumes, poorer recovery, and a 2.93-fold higher risk of severe disability at 90 days post-stroke (Albo et al, 2021).

Mitochondria within axons, a key organelle for energy production, are destroyed during axonal interruption, resulting in elevated ROS production and aggravating oxidative stress. This exacerbates WML-related cerebral hypoperfusion, increasing energy depletion, and induces ionic imbalances and excitotoxicity, eventually driving cell apoptosis and aggravating oxidative damage (Liu et al, 2021b).

Additionally, glymphatic system dysfunction is crucial in this pathological cycle. Severe glymphatic system dysfunction increases arterial and venous pressure, limiting the clearance of metabolic waste and enhancing the accumulation of pathophysiological products. Therefore, the accumulation of these products induces neu-

roinflammation and excitotoxicity, while increasing the risk of arteriovenous diseases and cerebral hemorrhage, both of which contribute to stroke recurrence (Guo et al, 2021; Park et al, 2021).

Immune responses also play a critical role in the pathophysiology of WMLs and stroke. After BBB disruption, peripheral immune cells such as neutrophils and monocytes infiltrate the brain, releasing reactive oxygen species and proteolytic enzymes that exacerbate white matter damage. Elevated levels of circulating pro-inflammatory cytokines, including IL-6, correlate with the severity of WMLs and poor stroke outcomes (Gertje et al, 2023; Monsour et al, 2023). These immune-mediated processes amplify glymphatic system dysfunction and establish a feedback loop that perpetuates neuroinflammation and white matter injury.

In summary, WMLs and stroke show a close relationship, with WMLs serving as an independent predictor of stroke and associated with post-stroke cognitive impairment and dementia (Jochems et al, 2023; Wang et al, 2021). Therefore, a hypothesis was proposed regarding a high correlation between WMLs and stroke pathophysiology. This pathological relationship between stroke and WMLs is not a simple one-way causal relationship but rather a vicious cycle in which they mutually exacerbate one another, leading to extensive neuronal death and neurological dysfunction.

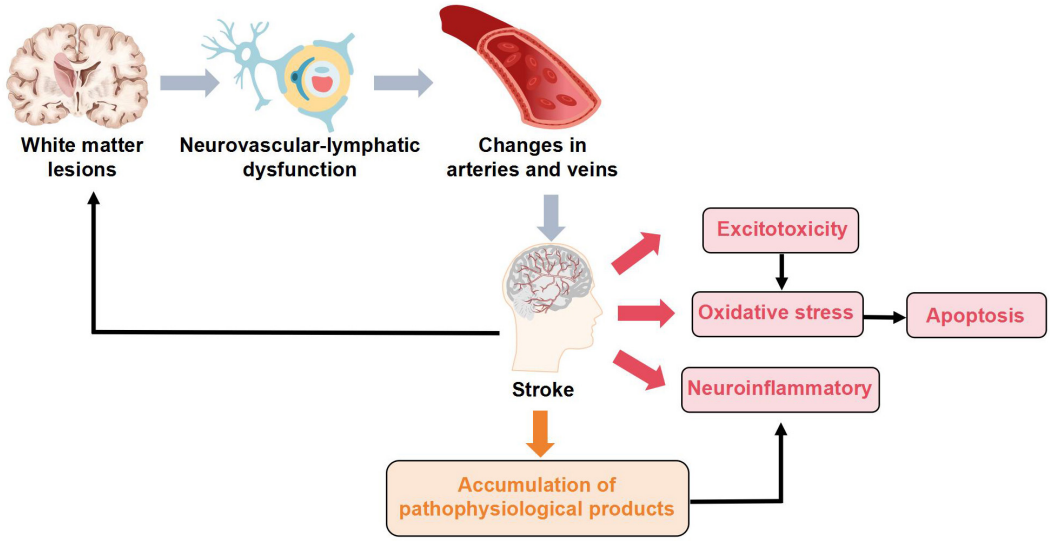

Fig. 4. A pathological relationship between stroke and white matter lesions. The figure was created via Adobe Illustrator 22.1.

Therapeutic Targets and Strategies for WMS

Effective management of WMS and WMLs requires a comprehensive understanding of disease progression and the integration of stage-specific therapeutic interventions. Tailoring management approaches to the acute, recovery, and sequelae phases allows for better alignment of treatment goals—such as preventing

recurrence, improving symptoms, and promoting neural repair—with the timing and mechanisms of these strategies, thereby improving their overall efficacy.

Acute Stage: Stabilizing the Condition and Preventing Further Damage

The primary goal in the acute phase is to restore cerebral perfusion and prevent secondary injuries. Reperfusion therapies, such as intravenous thrombolysis and mechanical thrombectomy, are standard treatments for IS (Berge et al, 2021). However, their use in patients with significant WML burden requires caution due to an increased risk of hemorrhagic transformation and poorer outcomes. Clinical study shows that patients with a high WML burden undergoing reperfusion therapies double the likelihood of experiencing hemorrhagic complications compared to those with lower burden (2.03, 95% CI 1.33–3.12) (Wang et al, 2022). Advanced imaging techniques, such as DTI and perfusion-weighted MRI, can guide in assessing tissue viability and predicting the risk associated with these treatments.

Anti-inflammatory treatments targeting acute neuroinflammation, such as IL-1β inhibitors or TNF-α blockers, have shown potential in preclinical models. For example, IL-1β inhibitors have indicated a 30% reduction in infarct size in animal models of IS (Edwards et al, 2020). These therapies mitigate the early inflammatory cascades exacerbating NVU and white matter damage. Furthermore, emerging nanoparticle-based delivery systems may enhance the precision and efficacy of these treatments by addressing challenges related to BBB.

Recovery Stage: Enhancing Neural Repair and Functional Recovery

During the recovery phase, interventions shift towards promoting neural repair and improving functional outcomes. Stem cell therapies, particularly those using mesenchymal stem cells (MSCs) and neural progenitor cells, have reported significant potential in this regard (Li et al, 2021). A network meta-analysis showed that bone marrow-derived mesenchymal stem cell therapy significantly reduced stroke-related mortality (RR 0.42, 95% CI 0.15–0.86), and significantly improved Medical Research Society (mRS) scores (Wang et al, 2024). These cells secrete neurotrophic factors, reduce oxidative stress, and stimulate remyelination, directly targeting the pathological mechanisms underlying WMLs and WMS. Early-phase clinical trials have indicated neurological recovery benefits, though challenges such as delivery methods, immune rejection risks, and long-term safety concerns persist (Qiu et al, 2023).

Rehabilitation plays an indispensable role in the recovery stage. Structured physical therapy, cognitive rehabilitation, and task-specific training are critical for addressing motor and cognitive deficits. Neuromodulatory techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have been shown to improve functional recovery by 25% when combined with traditional rehabilitation approaches (Bolognini et al, 2020). Patients with extensive ischemic damage or severe WML burden may benefit from incorporating these interventions with stem cell therapy for synergistic effects.

Sequelae Stage: Preventing Recurrence and Managing Chronic Effects

The sequelae stage focuses on secondary prevention and the management of long-term complications. Antiplatelet agents, such as aspirin and clopidogrel, remain a cornerstone of secondary prevention treatment. Furthermore, statins play a critical role by stabilizing atherosclerotic plaques and improving endothelial function, reducing recurrent ischemic events by 33%, and slowing WML progression, making them a valuable option for high-risk patients (Katsanos et al, 2020).

Integration Across Stages

Integrating strategies across various stages of management requires combining advanced diagnostic and therapeutic tools. Imaging modalities, such as dynamic contrast-enhanced MRI and functional MRI, combined with biomarkers, enable more accurate risk stratification and personalized treatment plans. For example, combining NFL levels with DTI data improves the prediction of cognitive decline in WML patients by 30% compared to imaging alone (Schultz et al, 2020).

Emerging therapeutic strategies, including stem cell interventions and anti-inflammatory treatments, hold promise in preclinical studies. Stem cell therapy promotes neural repair by secreting neurotrophic factor, regenerating myelin, and restoring neurovascular function. Anti-inflammatory treatments targeting microglial activation and cytokine release have effectively reduced neuroinflammation. However, clinical translation of these approaches faces challenges, such as concerns regarding safety, patient selection, and optimization of delivery methods. Recent clinical trials reveal mixed results; for instance, while stem cell therapies have improved neurovascular repair, their long-term efficacy remains inconclusive due to variability in patient responses and delivery protocols (Bonsack et al, 2020). Standardized clinical trials with well-defined endpoints are critical to resolve these inconsistencies.

Personalized medicine represents a promising direction for addressing the heterogeneity of WML pathology and stroke outcomes. Advances in genomic and proteomic profiling allow the identification of patient subgroups with distinct pathological features, enabling targeted interventions that optimize efficacy and reduce adverse effects. For example, recent research has highlighted that genetic polymorphisms in cytokine pathways impact patients' response to anti-inflammatory therapies, underscoring the potential for stratified treatment approaches (Nikolic et al, 2020; Zhang et al, 2022b). Similarly, precision drug delivery systems, such as nanoparticle-based platforms, offer innovative solutions for overcoming blood-brain barrier challenges, thereby enhancing the bioavailability of therapeutics in affected brain regions (Lu et al, 2021; Thangudu et al, 2020).

Conclusion

Stroke, the second leading cause of mortality worldwide, causes significant economic burdens. WMLs are closely related to stroke in terms of shared epidemiology and risk factors. However, the underlying pathophysiology between WMLs and stroke differs significantly. While the pathophysiology of WMLs remains a

matter of debate, current studies indicate that NVU dysfunction and glymphatic system impairment jointly contribute to their progression. Based on this understanding, the pathological relationship between stroke and WMLs was inferred. Additionally, an overview of the common treatment for WMS underscores the challenges in managing these conditions.

Despite the advancement in pathophysiology, treatment, and rehabilitation of stroke and WMLs over the past few decades, the association between these conditions remains poorly understood. Particularly, the lack of consensus on the pathophysiology of WMLs significantly hinders clinical study and treatment innovation for stroke and WMLs. Additionally, breakthroughs in treating patients with WMS have been limited, emphasizing the need for further investigation. WMLs, as a radiological indicator strongly associated with stroke, warrant more extensive research into their pathophysiological mechanisms.

Future research should prioritize large-scale, multicenter clinical trials to validate emerging therapies, as well as integrate biomarkers and precision medicine into routine clinical practice. Bridging the gap between basic research and clinical application will facilitate the development of personalized, effective treatments, ultimately improving the quality of life for individuals affected by WMLs and stroke.

Key Points

- White matter disease serves as an independent risk factor for stroke and plays a crucial role in its prognosis.
- There is a potential pathological link between stroke and white matter lesions.
- Elucidating treatment strategies and identifying potential therapeutic targets for white matter stroke can effectively enhance quality of life for these patients.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

XP, ZM, ZL and JG designed and undertook this review. XP, ZM, ZL and JG drafted the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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