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Research Progress on the Correlation between the Total Imaging Load and the Damage Caused by Cerebral Small Vessel Disease

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Abstract: *Cerebral small vessel disease (CSVD) encompasses a spectrum of clinical, imaging, and pathological alterations resulting from diverse cerebrovascular pathologies affecting arteries, arterioles, capillaries, and venules. As a primary etiology of lacunar infarcts, white matter hyperintensities, and vascular injury, CSVD typically manifests as acute stroke, cognitive impairment, neuropsychiatric symptoms, and motor disorders. Early clinical detection remains challenging due to non-specific presentations, often leading to delayed diagnosis until symptom onset. Prognosis is generally unfavorable, significantly compromising functional independence. Proactive screening and intervention may decelerate progression and enhance quality of life. This review synthesizes contemporary research on correlations between total imaging burden and cognitive deficits, motor dysfunction, affective disorders, voiding dysfunction, and dysphagia, offering actionable insights for early CSVD diagnosis/management while advancing innovative diagnostic and preventive paradigms.*

Keywords: *CMB = Cerebral Microhemorrhage, CSVD = Cerebral Small Vessel Disease, MRI = Magnetic Resonance Imaging, PVS = Perivascular Space, VCI = Vascular Cognitive Impairment*

1. Introduction

Cerebral small vessel disease (CSVD) is a clinical entity characterized by structural and functional impairments of intracranial arteries, veins, and capillaries[1].It manifests with insidious onset, progressive deterioration, and multifaceted clinical presentations that challenge early diagnosis. CSVD exhibits gradual progression toward multidimensional dysfunction encompassing cognition, motor control, and affective regulation. Its prolonged course and subtle early symptoms often lead to patient neglect, while aging significantly elevates prevalence - affecting nearly 60% of individuals over 60 years and approaching 100% in nonagenarians [2]. Accelerated population aging, combined with rising rates of diabetes, hypertension, and dyslipidemia (key CSVD risk factors), has substantially increased its global burden. CSVD patients frequently develop cognitive impairment, motor disorders, and affective disturbances [3] - major contributors to functional decline in the elderly and increased familial caregiving demands. Recent research has particularly focused on CSVD-cognition relationships. Clinical trials indicate that approximately 80% of adults over 65 exhibit either clinical or neuroimaging evidence of CSVD[4].Magnetic resonance imaging (MRI) serves as the most reliable and accessible diagnostic modality, enabling early CSVD detection and management. Characteristic MRI markers include: Recent small subcortical infarcts, Lacunar infarcts, White matter hyperintensities (WMH), Enlarged perivascular spaces (EPVS), Cerebral microbleeds (CMB), Cerebral atrophy[5]; These features may occur individually or in combination. The varying degrees of correlation between imaging abnormalities and clinical manifestations provide critical insights into CSVD pathogenesis and modifiable risk factors. While individual MRI markers of CSVD demonstrate independent associations with concurrent gait disturbances, these radiological features rarely occur in isolation. Evidence indicates that the total CSVD burden score—derived from composite quantification of singular biomarkers on MRI—may more comprehensively reflect the global cerebral impact of CSVD and provide superior representation of the disease pathology[6].

2. Assessment Methods for Total Neuroimaging Burden

Conventional MRI in cerebral small vessel disease (CSVD) patients reveals four core neuroimaging

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biomarkers per STRIVE-2 criteria: white matter hyperintensities (WMH), lacunar infarcts (LACI), cerebral microbleeds (CMBs), and enlarged perivascular spaces (EPVS) [5]. The total CSVD burden quantitatively represents cumulative effects of these distinct MRI features and demonstrates predictive value for recurrent stroke post-ischemic stroke. Improved quantification of total cerebral CSVD burden may enable more effective patient stratification in clinical practice[7], facilitating early intervention and enhancing quality of life through personalized management pathways.

3. Clinical Manifestations of Cerebral Small Vessel Disease-Induced Injury

3.1 Cognitive Dysfunction

3.1.1 Overview of Cognitive Impairment

Cognitive function refers to the psychological capacity system enabling human brains to receive, process, store, and utilize information, comprising six core domains: attention, memory, executive function, language processing, visuospatial abilities, and reasoning. Its neurobiological foundation relies on dynamic neural networks involving the prefrontal cortex (decision-making), hippocampus (memory consolidation), and parietal lobes (spatial processing).Vascular cognitive impairment (VCI) constitutes a progressive cognitive deficit syndrome triggered by cerebrovascular pathologies – including cerebral infarction, intracranial hemorrhage, or chronic cerebral small vessel disease (CSVD) – or cardiovascular disorders causing cerebral perfusion abnormalities. This cognitive continuum ranges from Vascular Mild Cognitive Impairment (VMCI) to Vascular Dementia (VD), with CSVD representing the predominant etiology of VMC[5]. Approximately 50% of vascular dementia cases are attributable to CSVD pathology[8]. Current studies demonstrate that 30%-64% of CSVD patients exhibit varying degrees of cognitive impairment[9], with manifestation heterogeneity across neuroimaging phenotypes. Pathologically, CSVD induces white matter lesions and microinfarcts that disrupt neural signaling pathways. Within the cognitive domain, primary deficits involve executive dysfunction and reduced processing speed, clinically manifesting as impaired decision-making and psychomotor slowing. Progressive deterioration subsequently affects episodic memory and other cognitive domains, correlating with cortical-subcortical disconnection severity.

3.1.2 Correlations between Cognitive Impairment and Heterogeneous Neuroimaging Manifestations with Integrated Burden

Cerebral small vessel disease (CSVD) constitutes a primary etiology of ischemic/hemorrhagic stroke and vascular cognitive impairment[10]. White matter hyperintensities (WMH), a hallmark CSVD neuroimaging manifestation, critically contribute to cognitive decline across the continuum from subjective cognitive decline to mild cognitive impairment and vascular dementia [11].

Clinical studies demonstrate that WMH-induced cognitive deficits correlate with disconnection of white matter tracts within frontoparietal networks [12]. Pathophysiological mechanisms involve: Subcortical WMH disrupting prefrontal-subcortical circuits and cortico-cortical connectivity[13], impairing conduction efficiency and processing speed Prefrontal WMH causing cortical hypometabolism and atrophy [14], WMH-induced cholinergic pathway degeneration [15], cerebral hypoperfusion [16], and progressive atrophy [17].WMH burden severity directly correlates with cognitive impairment magnitude across multiple domains (memory, executive, comprehension [18]. Prospective cohort studies confirm WMH progression predicts vascular cognitive impairment (VCI) [19], consistent with Li et al. [20]. After covariate adjustment, total WMH volume significantly associates with global cognition and domain-specific deficits (memory, executive, visuospatial, language, attention). Cerebral microbleeds (CMBs): Total burden independently correlates with attention/executive dysfunction and verbal fluency deficits [21].

Lin et al. [22] demonstrated that cerebral microbleeds (CMBs) - including their presence, progression rate, quantity, and distribution (particularly in the temporal lobe) - exhibit significant correlations with cognitive decline. These findings implicate CMBs in the pathological processes underlying cognitive impairment.

In a cross-sectional study of hypertensive populations by Zhang et al. [23], CMB presence and increased quantity independently associated with mild cognitive impairment (MCI) in essential hypertension patients without prior transient ischemic attack (TIA) or stroke history. Jie et al. [24] established through risk factor-adjusted meta-analysis that enlarged perivascular spaces (EPVS) burden correlates with cognitive impairment, suggesting EPVS may serve as a harbinger of cognitive

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dysfunction. In a study of the elderly population by Libecap et al. [25], it was stated that the burden of EPVS in the elderly was negatively correlated with the performance on the Montreal Cognitive Assessment (MoCA), which is a standardized clinical measure of global cognitive function. Additionally, the EPVS burden was positively correlated with the volume of white matter hyperintensities (WMH), which is an established marker of cerebral small vessel disease (CSVD).In the study by Li et al. [26], it was also demonstrated that cerebral atrophy was closely related to CSVD - associated cognitive decline.

3.2 Motor Dysfunction

3.2.1 Overview of Gait Abnormalities

Cerebral small vessel disease (CSVD) represents a prevalent cerebrovascular disorder in the elderly, manifesting dichotomously: acute vascular occlusion causing stroke versus insidious chronic progression of neurological deficits. Gait disturbance ranks as the second most common CSVD complication after cognitive impairment [27], frequently co-occurring with cognitive decline. Patients exhibit gait instability characterized by shortened stride length, reduced gait velocity, and significantly elevated fall risk. The core pathogenesis involves CSVD-induced sensorimotor integration deficits, resulting in impaired dynamic balance control during ambulation and abnormal three-dimensional kinematic parameters. A pivotal study [28] established direct correlations between CSVD and limb rigidity, tremors, and postural instability. These gait abnormalities substantially diminish quality of life, escalate caregiver economic burden, and increase accident-related mortality.

3.2.2 Genetic factors in cerebral small vessel disease and their impact on stroke and dementia

Cerebral white matter facilitates neural signal transmission and coordinates functional integration across brain regions. White matter hyperintensities (WMH) disrupt axonal integrity within these pathways, impeding information transfer. Evidence indicates rapid WMH progression – particularly periventricular WMH – correlates with lower limb motor impairment [29]. WMHs predominantly in deep regions induce motor incoordination by disrupting neurotransmission pathways.

Cerebral microbleeds (CMBs), resulting from microvessel rupture, damage neural conduits when affecting basal ganglia or brainstem. This pathway disruption obstructs motor command transmission, precipitating motor dysfunction.

In a study by Yutong Hou et al[30]., it was indicated that enlarged perivascular spaces (EPVS) can cause deterioration of gait and upper - limb function. Different imaging manifestations of cerebral small vessel disease (CSVD) act in different ways and to different degrees. The total imaging burden comprehensively assesses the imaging lesions of CSVD, allowing for a more intuitive and three - dimensional understanding of the functional impairments caused by CSVD lesions. In a study by Yutong Hou et al. [30] involving 227 participants, the analysis showed that gait performance was negatively correlated with the total magnetic resonance imaging (MRI) CSVD burden. The total CSVD burden was positively correlated with step width and cadence and negatively correlated with step length. However, since the subjects in this study were from a single center, the generalizability of the research results to the general population may be limited. CSVD severity directly associates with gait abnormalities, fall history, and future fall risk[31]. CSVD prevention should constitute an integral component of public health strategies to enhance mobility and reduce fall-related morbidity in aging populations.

3.3 Affective disorders

3.3.1 Overview of Affective Disorders

Cerebral small vessel disease (CSVD) precipitates neuropsychiatric symptoms including depression, anxiety, and apathy. Depressive disorder manifests as persistent low mood accompanied by social withdrawal, appetite loss, and sleep disturbances. Anxiety disorder primarily features irritability and tension with somatic symptoms (tremors, palpitations, postural instability, cold sweats, dizziness/headache, gastrointestinal distress). Apathy syndrome is characterized by blunted affect, diminished facial expressivity, reduced motivation/interest, and requiring continual prompting for daily activities. The pathophysiological mechanism involves CSVD-induced damage to cortico-striato-thalamic circuits, disrupting neurotransmission regulation and precipitating aberrant emotional modulation.

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3.3.2 Correlations between Affective Disorders and Heterogeneous Neuroimaging Manifestations with Integrated Burden

Neuropsychiatric symptoms (NPS) are prevalent in individuals with cognitive impairment, including Alzheimer's disease (AD), dementia, and mild cognitive impairment (MCI). Evidence demonstrates that NPS correlate with accelerated cognitive decline[32], poorer prognosis[33], and reduced quality of life[34]. Based on symptom clustering, specific NPS may aggregate into latent subsyndromes[35; 36]. The European Alzheimer's Disease Consortium proposed four neuropsychiatric subsyndromes from large AD cohorts: hyperactivity, psychosis, affective symptoms, and apathy [37].

Cerebral microbleeds (CMBs) – a neuroimaging biomarker of cerebral small vessel disease (CSVD) – associate with hyperactivity and higher Neuropsychiatric Inventory (NPI) total scores, exacerbating specific psychiatric symptoms [38; 39]. In a cohort study, Xu et al. observed correlations between CMB presence and apathy/depression [39]. Furthermore, studies establish relationships between SVD burden and multiple NPS, indicating vascular pathology's role in driving psychiatric manifestations[40].The pathophysiological mechanism involves SVD-induced neurodegeneration and neural disconnection[41; 42], which disrupts functional networks implicated in NPS[43; 44]. Apathy, fatigue, and delirium independently associate with greater white matter lesion burden [45].

3.4 Urinary disorders

3.4.1 Overview of urinary disorders

Voiding dysfunction refers to abnormalities in urinary elimination, primarily manifesting as dysuria, urinary frequency, urgency, and incontinence. Etiologies are diverse, including neurological disorders, urological diseases, medication side effects, among others. These symptoms substantially compromise patients' quality of life.

3.4.2 Correlations between Voiding Dysfunction and Heterogeneous Neuroimaging Manifestations with Integrated Burden

Cerebral small vessel disease (CSVD) precipitates voiding dysfunction, constituting one of its primary clinical manifestations. Current evidence indicates a 75% prevalence of urinary disorders among adults aged ≥65 years[46; 47]. CSVD induces cumulative chronic damage to micturition control centers – particularly through disruption of prefrontal-sacral cord pathways – initiating aberrant bladder regulation. As pathology progresses, detrusor overactivity manifests as urinary urgency and frequency; conversely, neural conduction failure may prevent effective central transmission of continence commands.

3.5 Dysphagia

3.5.1 Overview of Dysphagia

Dysphagia refers to impairment in the passage of food from the oral cavity to the stomach. Etiologies include oropharyngeal disorders, esophageal diseases, and neurological conditions. Clinical manifestations encompass effortful swallowing, choking sensation, and impaired nutritional intake, with severe cases precipitating aspiration and pulmonary complications. In cerebral small vessel disease (CSVD), white matter hyperintensities and lacunar infarcts damage central swallowing pathways – particularly through corticobulbar tract disruption and nucleus tractus solitarius ischemia – resulting in delayed pharyngeal reflex and elevated aspiration risk.

3.5.2 Correlations between Dysphagia and Heterogeneous Neuroimaging Manifestations with Integrated Burden

White matter hyperintensities (WMH) and enlarged perivascular spaces (EPVS) correlate with dysphagia severity. Higher WMH Fazekas grades and greater EPVS burden progressively impair swallowing function. Janina et al. [48] demonstrated that severe deep white matter hyperintensity (DWMH) scores associate with aspiration during swallowing, while increased basal ganglia EPVS correlate with prolonged oral transit time (OTT) and pharyngeal transit time (PTT). Given that swallowing is controlled by widely distributed bilateral neural networks, global brain tissue loss from cerebral atrophy increases the likelihood of disrupting critical swallowing regions and their coordination. Maeshima et al. [49] investigated the relationship between cerebral microbleeds (CMBs) and dysphagia using T2-weighted imaging for hypodense shadows (hemosiderin deposits). Results confirmed significant CMB-dysphagia associations, particularly with bilateral microbleeds. Zhang et al. [50] reported that dysphagia in patients with recent single subcortical infarcts (RSSI) correlates with more severe total cerebral small vessel

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disease (CSVD) burden on MRI. The global MRI CSVD burden score predicts dysphagia risk in this population.

4. Discussion

With accelerating population aging, the incidence of cerebral small vessel disease (CSVD) continues to rise. Characteristic manifestations include cognitive decline, motor dysfunction, affective disorders, voiding impairment, and impaired social functioning – collectively diminishing quality of life while increasing familial and societal burdens. Current CSVD research faces critical knowledge gaps regarding pathogenesis, clinical-imaging correlations, validated neuroimaging biomarkers, and standardized integrated burden assessment. As a whole-brain syndrome with heterogeneous complications, early diagnosis is paramount for disease control. However, reliance on a single imaging biomarker proves insufficient for timely detection. The baseline CSVD burden scoring system proposed by the Maastricht University Collaborative Group in 2013[51] has emerged as the gold-standard evaluation method in global clinical research. This approach mitigates overreliance on isolated biomarkers and confounding factors, enhancing early diagnostic accuracy. While MRI biomarkers remain indispensable, comprehensive clinical assessments are essential for auxiliary diagnosis. Given the current scarcity of effective CSVD treatments – with management focusing primarily on prevention – early risk factor identification and timely intervention are crucial to delay functional decline, improve quality of life, and alleviate psychological distress among patients and caregivers.

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