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Correlation of imaging markers of cerebral small vessel disease with left ventricular disease: A review

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Abstract: Cerebral small vessel disease (CSVD) is a combination of disorders that affects the small arteries, veins, and microvessels of the brain. It can be observed on cranial magnetic resonance imaging as cerebral white matter hyperintensity, enlarged perivascular spaces, cerebral microbleeds, cerebral atrophy, and lacunes. The underlying mechanisms of cerebral small vessel disease remain unclear. Recent studies have suggested that left ventricle-associated diseases can contribute to a better understanding of the pathogenesis of cerebral small-vessel disease. Epidemiologic and clinicopathologic data have uncovered evidence of a relationship between cerebral small vessel disease and left ventricular disease. The purpose of this paper is to explore the complex relationship between cerebral small vessel disease and left ventricular disease. Defining the relationship between cerebral small vessel disease and left ventricular-related diseases is crucial for early prevention of cerebral small vessel disease.

1. Introduction

Cerebral small vessel disease (CSVD) is a common manifestation of cerebrovascular disease that can seriously jeopardize one's health due to its insidious onset, mild clinical symptoms, and ease of neglect [1]. Early diagnosis can significantly reduce the mortality and disability of related cerebrovascular events. Risk factors for cerebral small vessel disease include age, genetics, gender, hypertension, diabetes mellitus, hyperlipidemia, hyperhomocysteinemia, smoking, and obesity. In addition, inflammatory factors, vascular endothelial dysfunction, altered anatomy of the blood-brain barrier [2], and hemodynamic disorders [3] are also associated with this condition. Despite years of research, the definitive pathophysiology of cerebral small-vessel disease has not been effectively demonstrated, and effective treatments remain unavailable. Various theories have been suggested to be related to the pathomechanism of CSVD since the later stages of CSVD lead to complex disorders such as cognitive impairment and gait disorders. Patients with CSVD are at an increased risk of stroke, dementia, and death [4]. The brain and heart share similarities in their vascular anatomy, distributing arterial conduits over the organ's surface to enable tissue perfusion and oxygen interaction through deep penetrating branch arteries. The arterial network system of the heart and brain contains numerous branches. Large arteries branch into medium arteries or continue

directly into small arteries, which in turn branch into even smaller arteries [5]. The heart, as the pumping organ of the systemic blood supply, has a close hemodynamic relationship with the left heart. Any structural or functional changes in the left atrium and left ventricle will impact systemic hemodynamics. In clinical practice, it has been observed that many patients with cerebral small-vessel disease also have left ventricular diseases, such as left-sided heart failure and structural abnormalities of the left heart. An understanding of the relationship between cerebral small-vessel disease and left ventricular diseases is important for the prevention and treatment of both conditions. This knowledge can guide the rational prevention and treatment of cardiovascular diseases caused by left ventricular diseases. Currently, there is a great deal of controversy regarding the correlation between CSVD and left ventricular disease. The purpose of this review is to describe the characteristics of left ventricular disease and the progress of research on its correlation with imaging markers of CSVD in order to establish a scientific basis for the early diagnosis of CSVD in the population.

2. The concept and the epidemiologic features

CSVD is a type of lesion in which micro and small arteries, their distal branches, capillaries, microvessels, and small veins [1] are the main responsible vessels in the brain. This category also includes some hereditary CSVD, such as autosomal dominant disease combined with subcortical infarcts and leukoencephalopathy (CADASIL) and autosomal recessive disease combined with subcortical infarcts and leukoencephalopathy (CARASIL). Recent epidemiological reports indicate that CSVD caused by small-artery occlusion accounts for approximately 30% of ischemic stroke cases in China [6].Diagnosis of this disease primarily relies on the examination of diseased brain tissue due to the heterogeneity of its clinical symptoms. Therefore, cranial MRI examination is crucial for patients with this disease. The Standardized Reporting Organization for Neuroimaging of Vascular Alterations (STRIVE) updated the diagnostic imaging criteria for the study of cerebral small-vessel disease in May 2023, known as the STRIVE-2 criteria[7], with neuroimaging manifestations that include cortical microinfarct, recent subcortical small infarcts(RSSI), perivascular space(PVS), presumed luminal spaces of vasculogenic origin, white matter hyperintensity(WMH), cerebral microbleeds(CMBs), cortical superficial siderosis(cSS), presumed small-vessel disease originating spontaneous cerebral hemorrhage, and brain atrophy.Left ventricular disease encompasses several pathologies, including left ventricular hypertrophy, mitral regurgitation, diastolic dysfunction, and heart failure with normal ejection fraction. Among these conditions, left ventricular hypertrophy is particularly common and occurs mainly due to hypertrophy and degeneration of cardiomyocytes in response to chronic stress or increased volume loading, resulting in left ventricular wall thickening and increased myocardial weight. Myocardial remodeling is considered the cause of this process and has been linked to genetic factors. Epidemiologic surveys show that left ventricular hypertrophy affects approximately 10% to 20% of the adult population [8, 9]. The prevalence of moderate to severe mitral regurgitation is even higher at 10% in the elderly population over 75 years of age [10], which underscores the high risk of this condition in the elderly population. Recently, research has focused on left ventricular diastolic dysfunction, which has been found to precede the onset of left ventricular systolic dysfunction and lead to abnormal myocardial function [11].

3. Correlation of imaging markers of CSVD with left ventricular disease

3.1. Lacune (of presumed vascular origin) and left ventricular disease

The lacune of presumed vascular origin is a common imaging manifestation of CSVD, usually

caused by occlusion of small penetrating arteries deep in the cerebral hemispheres or brainstem. This occlusion causes localized ischemia and hypoxia, necrosis, and liquefaction of brain tissue, resulting in the formation of a round or ovoid cavity that resembles cerebrospinal fluid[12]. In patients with hypertensive left ventricular hypertrophy, remodeling of the left ventricle during myocardial stages results in changes in myocardial coordination. Conversely, in patients with centripetal remodeling of the left ventricle, approximately 92% of patients experience elevated left ventricular end-diastolic pressure [13], which ultimately leads to changes in left ventricular motor function and hemodynamics. The relationship between the blood supply to the heart and the brain suggests that end-organ dysfunction may occur in parallel. A large cohort study demonstrated that structural and systolic dysfunction of the left ventricle increases the odds of lacunar cerebral infarction [14]. Some investigators have found that the left ventricular mass is greater in patients with lacunar lesions of brain tissue than in patients without these [15], and the explanation for this result is that hemodynamic changes produced by the increased left ventricular mass result in changes in the pulse wave velocity of the aortic arch, which has a weakened elastic mechanism for receiving per-beat output, and consequently produces a change in the stability of the amplitude of the downstream pulse wave, and, as the downstream-most or distal-most vessel, the of the brain penetrating small arteries are susceptible to lining damage and lead to thromboembolism [16, 17].Left ventricular ejection fraction is the most direct reflection of left heart function among all the indices. Changes in ejection fraction can lead to cerebrovascular disease. One study found a negative correlation between ejection fraction and lumen burden [18]. In a cross-sectional survey of ischemic strokes with atrial fibrillation, researchers found that a thicker posterior wall of the left ventricle was associated with a higher risk of cavitation [19].

3.2. WMH and left ventricular disease

The major site of WMH is located in the white matter area surrounding the deep ventricles of the brain, which is mainly supplied by the long cortical medullary branch and the deep penetrating branch of the white matter artery. Arteries in these areas are terminal arteries that are tortuous and spiral with little collateral flow, forming a watershed [20], which makes white matter in these areas very vulnerable to ischemia, leading to chronic vascular injury. From a hemodynamic perspective, there is a clear difference in blood flow between the gray matter and white matter of the brain. Due to poor vascular regulation in the white matter region, it is the first to be damaged when cerebral perfusion pressure drops for various reasons. According to previous research, WMH may be associated with cerebrospinal fluid blood circulation and altered permeability of the blood-brain barrier [2, 3]. The structural integrity of the brain's white matter is critical for maintaining cognitive function. When the white matter structure is damaged, cognitive function may be reduced to different degrees, which is manifested by slower information processing speed and weaker executive ability. In addition, the distribution of WHM correlates with the clinical manifestations of cognitive impairment.A cross-sectional study found that diastolic dysfunction in the left ventricle leads to changes in cardiac hemodynamics, resulting in decreased compliance of small cerebral arteries. This effect is particularly pronounced when echocardiography indicates a higher baseline level of WHM volume and faster progression when $E/e' \geq 15$ [21]. In a prospective longitudinal observational study, it was confirmed that in young adults, high-signal distribution in the white matter is associated with impairment of cognitive function, mainly manifested in slowed processing speed and executive ability. A correlation between left ventricular diastolic dysfunction and rate of progression of WHM in young adults with hypertension has been reported [22], which may be related to passive extracellular matrix changes or a cascading response of inflammatory factors. Studies have found variability in the pathologic manifestations of periventricular WHM and deep WHM [23,

[24]. This may explain the greater correlation of deep WHM with left ventricular hypertrophy than periventricular white matter hyper-signal in patients with left ventricular hypertrophy due to hypertension [25].In a cohort study of elderly individuals, an association was found between left ventricular structure and left ventricular systolic dysfunction with an increase in WHM. The volume of WHM increased differently with an increase in left ventricular wall thickness and left ventricular mass index [13]. Other studies have also confirmed a statistically significant association between higher left ventricula mass or left ventricula mass index and higher WHM volume [26].

3.3. CMBs and left ventricular disease

CMBs are subclinical brain parenchymal lesions caused by microvascular lesions, mainly characterized by small hemorrhages, approximately 2 to 5 mm in diameter, which appear as round or nearly round, well-circumscribed, homogeneous hypointense areas on T2*-weighted gradient-echo magnetic resonance imaging (GRE-T2*WI) and magnetic susceptibility-weighted imaging (SWI). CMBs in gray and white matter regions near the cortex may be indicative of cerebral amyloid angiopathy, whereas CMBs in deep brain and subcortical regions are frequently observed in patients with small artery atherosclerosis caused by chronic hypertension [27]. Recent studies have shown a strong correlation between left ventricular-related diseases and microhemorrhages. Additionally, some studies have found a negative correlation between ejection fraction and significant microhemorrhages [18, 28]. This may be due to the fact that left ventricular systolic dysfunction accelerates cerebral microvascular injuries and/or leads to the development of microhemorrhages. Further research is needed to develop more effective microhemorrhage detection techniques. Valvular disease affects the structure and function of the left ventricle progressively. Some researchers have found that left ventricular remodeling may hasten the progression of cerebral microhemorrhages in patients with aortic or mitral valve closure insufficiency [29].In a subset of hypertensive patients, the chronic stress response to long-term hypertension leads to anisotropic changes in left ventricular mass index and left ventricular geometry,which leads to hemodynamic disturbances in the intracerebral vasculature, a phenomenon that has been studied in which microvessels precede other imaging markers of cerebral small-vessel disease when there is a concentric row-type hypertrophy of the left ventricle [30].

3.4. PVS and left ventricular disease

PVS is a common imaging marker in patients with CSVD. With age, intracranial blood vessels deform, thicken, and twist to form fluid-filled round/oval or linear interstitial spaces, and many fine pinhole-like changes called sieve states can also form in white matter regions, usually around small perforating vessels in white matter or deep gray matter regions, usually with a maximum diameter of less than 3 mm [12]. A positive correlation was found between the visibility of the PVS and age. The basal ganglia region showed the strongest association with the visibility of the perivascular gap, after analyzing the correlation between the three main regions assessed, namely, the center of the semiovals, the basal ganglia region, and the hippocampus[31]. Among other risk factors for PVS, a negative correlation between left ventricular ejection fraction and PVS (P=0.002) has been proposed [18], which further reveals that the occurrence of hemodynamic disturbances can have an impact on the visualization of PVS. In order to delve into the intrinsic link between the PVS and the left ventricle, Del et al. carried out a study and found that there was a significant correlation between the PVS and systolic and differential pulse pressure in the basal ganglia region [32].

3.5. Brain atrophy and left ventricular disease

Brain atrophy is the reduction in brain tissue volume that is not related to focal brain injury, such as traumatic brain injury or cerebral hemorrhage, and is visible to the naked eye. Long-term follow-

up is necessary to recognize and assess the progression of cerebral atrophy. A case report of a patient with idiopathic dilated cardiomyopathy [33], who was admitted to the hospital with dyspnea and leg edema, had an echocardiogram suggesting an ejection fraction of 36%, imaging studies suggesting decreased blood-cerebral blood flow, and clinical symptoms suggesting significant cognitive brain dysfunction. This implies that low cardiac output may directly contribute to systolic heart failure as well as total cerebral cerebral atrophy.Research has shown that patients with left ventricular hypertrophy accompanied by type 2 diabetes mellitus exhibit more pronounced amygdala atrophy compared to those without type 2 diabetes mellitus. Additionally, the total brain volume also displays the same change [34]. Using an automated segmentation technique, the brain was divided into 132 regions. Six regions showed significant atrophy associated with heart failure with normal ejection fraction [35]: accumbens area, posterior insula, amygdala,cerebellar white matter, anterior orbital gyrus and angular gyrus. The regions of cerebral atrophy associated with CSVD overlap or intersect with those in other neurodegenerative diseases. Further investigation is needed to understand the spatial patterns between them and to address clinical problems.

4. Conclusions

In the field of medicine, there is increasing attention being paid to the link between cerebrovascular disease and cardiovascular disease. Specifically, the relationship between cerebral small-vessel disease and left ventricle-related diseases has been widely studied. Many studies have confirmed that hemodynamic disorders resulting from systolic and diastolic dysfunction of the left ventricle are a key factor in the development of CSVD. This research has yielded new insights into the pathogenesis of cerebral small-vessel disease. However, it has also raised several questions that require further investigation. For instance, the relationship between left ventricular disease and CSVD, the sensitivity and specificity of new blood markers in diagnosing CSVD in combination with left ventricular disease, and whether early intervention of left ventricular disease can slow down the progression of CSVD. To improve clinical practice, it is necessary to conduct a more in-depth study of the relationship between the two. This will aid in the development of individualized diagnostic and therapeutic plans for patients with cerebral small-vessel disease, which can help slow down the progression of clinical symptoms and provide effective preventive and curative measures.

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