Austin Journal of Clinical Neurology

Open Access

Austin Publishing Group

Review Article

Recent Findings in Clinical Features and Imaging of Cerebral Small Vessel Disease Related Gait Disorder: A Systematic Review

Yin Xd, Liu XY and Meng GL*

Neurorehabilitation Center, Department of Neurology, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, China

***Corresponding author:** Meng GL, Neurorehabilitation Center, Department of Neurology, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, No.301, Yan Chang Middle Road, Jing An District, Shanghai, 200072, China

Received: April 21, 2022; **Accepted:** May 24, 2022; **Published:** May 31, 2022

Abstract

Gait disorder is a common symptom of Cerebral Small-Vessel Disease (CSVD). A large proportion of CSVD patients have gait disorders, which can cause falls in elderly individuals and increase the probability of death. A variety of neurological diseases may be associated with gait disorders. Gait disorders caused by CSVD may exhibit distinct clinical characteristics such as gait speed, stride length, and dual-task walking, which require further study. Visualizing CSVD pathologies *in vivo* is challenging, therefore the diagnosis of CSVD has relied on imaging findings. However, traditional imaging markers cannot accurately predict clinical manifestations of gait disorders in patients with CSVD. This review summarizes recent findings on the clinical features and imaging of CSVD-related gait disorders and aims to provide future research directions.

Keywords: Cerebral Small Vessel Disease; Cognition; Gait Disorder; Imaging Markers

Introduction

Cerebral Small Vessel Disease (CSVD) is a syndrome characterized by clinical, imaging, and pathological findings that are thought to result from pathologies of the small cerebral vessels. Small cerebral vessels include perforating arterioles, venules, and capillaries. Typically, CSVD involves arterioles [1]. CSVD describes a series of imaging changes, including Recent Subcortical Small Infarct (RSSI), Lacunar Infarctions (LI), White Matter Hyperintensity (WMH), Cerebral Microbleed (CMB), Enlarged Perivascular Spaces (EPVS), and Cerebral Atrophy (CA) [2]. Small vessel diseases exhibit different types of etiologies. Pantoni proposed a simplified etiopathogenic classification, including arteriosclerosis (or age-related and vascular risk factor-related small vessel diseases), sporadic and hereditary Cerebral Amyloid Angiopathy (CAA), inflammatory and immunologically mediated small vessel diseases, venous collagenosis, and other small vascular diseases. Arteriolosclerosis and sporadic and hereditary cerebral amyloid angiopathies are the most prevalent forms [1].

Because the mode of onset is unclear, little attention has been focused on CSVD despite a large population of patients. CSVD accounts for 45% of dementia and 25% of lacunar stroke cases, leaving 20% of patients disabled [1]. The incidence of CSVD correlates with sex and age. The incidence and severity of leukodystrophy (a type of CSVD) increases with age. Moreover, the severity of leukodystrophy tends to be higher in women than in men [3].

With the steady increase in life expectancy worldwide, the incidence of age-related CSVD is increasing, affecting approximately 5% of people aged 50years and almost all people >90 years, resulting in a huge social and economic burden [4]. Studies have shown that in the elderly >65 years of age, the incidence of cerebral diffuse white matter lesions can reach 27%-87%, and the incidence of LI is 6%-20%. Moreover, the incidence of CMB is 17.8% in people aged 60-69 years, and 38.8% in people ≥80 years of age [5].

CSVD often exhibits a latent onset with non-specific clinical manifestations, including stroke and symptoms of chronic progressive neurological impairment, including dementia, cognitive decline, gait disorder, and mood disturbance. Alternatively, CSVD may present with no symptoms, and only be discovered by chance on brain Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) examination [6-8]. In addition, clinical symptoms of CSVD are often highly inconsistent in nature and severity among patients with similar degrees of CSVD on brain imaging. CSVD is considered an important contributor to early vascular dementia, and 45% of dementia cases are associated with it [4]. Gait disorders occur in 35% of patients with CSVD, and it is an independent risk factor for Parkinson's disease (PD) [9]. Some researchers have classified movement disorders in patients with CSVD as "Parkinson's syndrome" [10,11], but a difference in gait disorders is observed between the two diseases. To some extent, gait disorder in CSVD mainly manifests as motor dysfunction, including reduced stride, balance disorders, and falling tendency, whereas myotonia and cogwheel rigidity are infrequent. Notably, it is also perceived as a "lower-body Parkinson's disease".

Clinical Features of CSVD-related Gait Disorder

Gait Characteristics

Gait refers to the form and posture of walking and standing. More than half of the patients with radiographically confirmed CSVD have gait disorders. However, CSVD has little effect on overall motor functions and the ability to perform daily activities. Gait disorders are mainly characterized by slow speed, dragging, wide strides, and different bilateral step lengths. However, other studies have found that gait disorders in patients with CSVD show only slight rhythm defects

Citation: Yin Xd, Liu XY and Meng GL. Recent Findings in Clinical Features and Imaging of Cerebral Small Vessel Disease Related Gait Disorder: A Systematic Review. Austin J Clin Neurol 2022; 9(1): 1156.

and speed reduction. Instead, age may play a major role in elderly patients with CSVD [12]. After excluding the effects of age, sex, and education level, some studies found that while completing Single-Task Walking (STW) and Dual-Task Walking (DTW) tests, elderly patients with CSVD showed a significantly shorter and slower stride length, higher Gait Asymmetry (GA), and higher phase coordination index (PCI) than those without CSVD. In addition, CSVD patients were more likely to have gait disorders, and the stability, symmetry, and coordination of gait were reduced while completing DTW [13].

Other Clinical Manifestations

In addition to gait disorders, cognitive decline is a common clinical manifestation of CSVD. Moreover, there may be a relationship between cognitive decline and gait disorder. Correlational research has found that brain resource allocation between cognition and gait has a certain influence on gait stability, and that a nervous system network connection exists between cognition and gait. This suggests that elderly patients with CSVD can maintain gait stability by reducing gait speed or increasing response time to cognitive tasks, whereas patients with PD reduce gait stability but prioritize cognitive tasks in DTW. In a cross-sectional study, Van de Schraaf et al. found that reduced gait and thinking speed, and mood were closely related to CSVD [14]. Cai et al. found that the white matter connection subnetwork related to gait and cognition is mainly in the frontal tract. When disrupted, cognitive function affects gait function in the elderly with CSVD [15].

The Mechanism of CSVD-Related Gait Disorder

As previously mentioned, gait refers to the form and posture of walking and standing. These activities are regulated by multiple systems including sensory, motor, and cognitive systems. Consequently, abnormal gait and balance in the elderly usually result from multiple factors. CSVD can affect nervous system function by damaging the cerebral cortex and critical nerve fiber connections in the white matter and deep gray matter, leading to different types and degrees of gait disorders.

Studies have shown that CSVD-related gait disorders are associated with cerebral lobe lesions. The frontal lobe contains the cortical motor and premotor areas, which control movement and are also related to cognitive and executive functions controlled by the anterior frontal lobe. The parietal lobe contains sensory areas related to perception of touch, pressure, temperature, and pain. The temporal lobe controls vision. All of these lobes are functionally related to gait control. In addition, the thickness of the cerebral cortex affects gait regulation. De Laat et al. found that the cortical thickness of the orbitofrontal and ventrolateral prefrontal cortex, inferior parietal lobe, cingulate gyrus, and visual association cortex were positively correlated with stride length. Additionally, the thickness of the primary, auxiliary motor, and cingulate cortexes was positively correlated with gait rhythm, whereas the thickness of the orbitofrontal cortex, ventrolateral prefrontal cortex, anterior cingulate cortex (especially the inferior parietal lobe), and superior temporal gyrus was negatively correlated with stride length [16]. Kim et al. found that gait score was correlated with the frontal and parietal lobes, and the bilateral corpus callosum. The gait score was also correlated with thinning of the bilateral frontal and lateral temporal parietooccipital cortex [17]. However, each functional area of the brain lobe does not operate alone, and the fulfillment of complex motor functions requires white matter fibers to connect multiple functional areas of the brain for nerve impulse conduction and information exchange. Consequently, impairment of white matter fiber integrity affects the regulation of motor function. Multiple studies have found that gait and postural abnormalities occur when White Matter Hyperintensities (WMH) affect important fibers (fasciculi thalamocorticales, corticospinal tract, corpus callosum, cingulate gyrus, etc.) [18-20]. White matter lesions and cortical thinning have been associated with gait disorders [17]. Deep White Matter Lesions (DWMH) play a more important role in gait disorders, because the distribution of white matter bundles is denser around the brain ventricle than it is in the deep brain. Structural changes in the deep brain may lead to gait disorders. Deep brain structures include the basal ganglia and the thalamus. The basal ganglia, cerebral cortex, and cerebellum coordinate to regulate voluntary movement, muscle tension, and postural reflex, and also participate in the regulation of complex behaviors. The thalamus receives input from the cerebellum and basal ganglia fibers and is connected to the frontal motor cortex to regulate body movement. This is an important node in the frontal-subcortical circuit. Several studies have shown that impairments of the basal ganglia and thalamus are associated with gait disorders. Karim et al. established a multiple regression model and found that lower resting state connectivity in basal ganglia regions is associated with slower gait speed [19]. Koblinsky et al. found that lower thalamic blood flow is associated with slower stride velocity in the elderly with CSVD [21]. Su et al. found that thalamic atrophy plays an important mediating role in CSVD, affecting walking speed in the elderly [22]. Iseki et al. found that abnormalities in the basal ganglia-thalamo-cortical loops partly explain the gait disorders observed in patients with Age-Related White Matter Change (ARWMC) [18].

The presence of CSVD can aggravate gait disorders in PD [23,24], but the mechanism of interaction between the two diseases is unclear. Currently, research has confirmed that CSVD is closely related to PD motor symptoms [24], which may provide new research directions for exploring the etiology of CSVD in the context of PD.

Advances in Imaging Research of CSVD-Related Gait Disorders

Multi-angle analysis of comprehensive imaging data during clinical follow-up may be the best method to describe the course of CSVD. Previous studies showed that various types of CSVD markers revealed by imaging including RSSI, LI, WMH, CMB, EPVS, and CA can all cause gait disorders. Combinations of CSVD markers can strongly predict future gait disorders in healthy older adults, with WMH and EPVS being the most likely factors [25].

Advances in Imaging Technology and New Markers

In addition to traditional imaging markers, novel imaging markers that can reflect CSVD-related gait disorders have been found. Diffusion Tensor Imaging (DTI) is a new functional magnetic resonance imaging technology based on Diffusion-Weighted Imaging (DWI). DTI can be used to measure the integrity of white matter fibers. Charlton et al. found that DTI was sensitive to ultrastructural changes in the white matter and could be used to monitor white matter changes within a short time [26]. The ability to visualize nerve fibers on DTI may enable gait evaluation in patients with CSVD. Van

der Holst et al. used DTI to analyze multiple white matter regions and found that stride decline was significantly associated with decreased Fractional Anisotropy (FA) and increased mean diffusivity. The effect was strongest in the corpus callosum and radiographic crown, and was independent of traditional markers of CSVD [27].

Ultrasound imaging has enabled the detection of substantia nigra hyperechogenicity, brain stem raphe hypoechogenicity, ventricle diameters, and sonographic characteristics of other brain structures on transcranial sonography. These characteristics can serve as biomarkers for a range of neurological diseases. Pavlović et al. compared neurological, cognitive, and emotional states, as well as transcranial ultrasound and magnetic resonance imaging in 102 patients with CSVD and 45 age- and sex- matched healthy control participants. They found that CSVD patients had a higher risk of brain stem raphe hypoechogenicity, substantia nigra hyperechogenicity, and enlarged third ventricles. Among them, substantia nigra hyperechogenicity was the most frequent condition found in patients with CSVD-related gait disorders [28].

Endothelial dysfunction is central to the early development of CSVD [29]. Therefore, application of advanced neuroimaging methods to reflect quantitative endothelial functional information may aid in predicting the occurrence and development of CSVD. Some indicators, such as cerebrovascular reactivity, Cerebral Blood Flow (CBF) and pulsatility, and Blood Brain Barrier (BBB) integrity can reflect endothelial function. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can reveal BBB leakage and multiple studies have shown that BBB leakage is associated with CSVD [30]. Endothelial injury can promote white matter injury, which is closely related to gait disorders as confirmed by previous studies. Therefore, the quantitative detection of BBB leakage could provide a future research direction for predicting CSVD-related gait disorders.

Retinal vascular parameters obtained by Optical Coherence Tomography (OCT) have also been proposed to reflect CSVD-specific pathological lesions such as endothelial injury, microglial activation, and axonal injury [31]. Multiple studies have confirmed an association between retinal vessels and CSVD [32-34]. The retina wall-to-lumen ratio (WLR) of the superior branch of the retinal artery was found to be significantly associated with the volume of WMH in CSVD, and also other markers of vascular integrity, microglial activation, and nerve axis injury [35].

Advances in Traditional Imaging Markers

WMH can be divided into two types according to the site of occurrence: Periventricular White Matter Hyperintensity (PVWMH), and DWMH. Gait disorders caused by CSVD are mainly related to the volume and distribution of the WMH. Smith et al. assessed cognition, gait, and MRI images in 803 community participants and found that a higher volume of supratentorial WMH was associated with a slower-timed gait and lower volumes of the supratentorial cortex, white matter, and cerebellum [36]. Pinter et al. found that WMH volume was associated with future gait disorders, independent of demographic factors, physical condition, and other cardiovascular risk factors [37]. It has been confirmed that PVWMH and supratentorial WMH may be more related to CSVD gait disorders because the distribution of white matter fiber bundles is denser around the cerebral ventricles than it is in the deep brain. Kim et al. found that PVWMH was associated with gait score, whereas total WMH or DWMH were not [17].

Gait disorders in patients with CSVD are primarily associated with the number of CMBs. Sullivan et al. found that a slower gait speed is related to the number of CMBs. Moreover, the co-existence of CMB and WMH may amplify the clinical manifestations. Choi et al. found that the presence of microbleeds magnified the adverse correlation between white matter lesions and gait [38].

The EPVS is an imaging marker of CSVD and is associated with cognitive decline in healthy elderly people. Gait disorders caused by CSVD are reflected in the number of white matter EPVS. Kubota et al. measured central motor conduction time (CMCT), an indicator of motor evoked potential (MEP) pyramidal tract dysfunction, and found that CMCT correlated with the number of white matter EPVS in the symptomatic brain hemisphere [39]. Additionally, the number of EPVS was associated with other imaging markers. For example, Laveskog et al. found that the number of perivascular spaces, especially the number of perivascular spaces in the basal ganglia, was associated with the degree of WMH in the brain lobes and deep brain [40].

Advances in Identifying the Relationship Between Cognition and CSVD Image-Related Gait Disorders

The regulation of gait is a highly cognitive process. Consequently, the study of gait disorders in elderly patients with CSVD should consider the key role played by cognition, since imaging-related cognitive impairment and gait disorder are correlated. Multiple studies have demonstrated that WMH volume is associated with cognitive decline and dementia [41], which in turn affect gait regulation. This may indicate that walking speed and cognitive decline in the elderly share a common neuropathological basis. However, in another study of middle-aged and elderly people, CMB and LI were associated with walking speed but not cognitive competence [42]. Clearly, the correlation between cognition and gait requires further investigation.

Conclusions

CSVD affects most of the elderly in the world, but its occurrence is insidious and difficult to detect. However, with continuing findings of clinical features and development of imaging markers, CSVD can be diagnosed earlier, making intervention and reversal in the early stages of the disease possible. Although the imaging classification of CSVD has been widely accepted, many questions still remain regarding its relationship with the pathogenesis of CSVD. Therefore, advanced neuroimaging quantitative techniques are needed to extract more useful CSVD imaging-feature measures (such as describing the shape of WMH and lacunes) to facilitate the study of CSVD mechanisms. The availability of new imaging technologies such as DTI, DCE-MRI, high-resolution vascular wall imaging (VWI), blood oxygen level-dependent scanning, and ultra-high field MRI continues to improve, providing a technical basis for further exploration of new imaging markers of gait disorders caused by CSVD. Additionally, another promising future area of research is that of serum biomarkers which have shown a preliminary association with CSVD.

References

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical

characteristics to therapeutic challenges. Lancet Neurol. 2010; 9: 689-701.

2. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013; 12: 822-838.
3. de Leeuw FE, de Groot JC, Achten E, Oudkerk M, Ramos LM, Heijboer R, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry. 2001; 70: 9-14.
4. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease A clinical review. Neurology. 2019; 92: 1146-1156.
5. Pinter D, Enzinger C, Fazekas F. Cerebral small vessel disease, cognitive reserve and cognitive dysfunction. J Neurol. 2015; 262: 2411-2419.
6. de Laat KF, van Norden AG, Gons RA, van Oudheusden LJ, van Uden IW, Bloem BR, et al. Gait in elderly with cerebral small vessel disease. Stroke. 2010; 41: 1652-1658.
7. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. Bmj. 2010; 341: c3666.
8. van Agtmaal MJM, Houben A, Pouwer F, Stehouwer CDA, Schram MT. Association of Microvascular Dysfunction with Late-Life Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017; 74: 729-739.
9. Hatate J, Miwa K, Matsumoto M, Sasaki T, Yagita Y, Sakaguchi M, et al. Association between cerebral small vessel diseases and mild parkinsonian signs in the elderly with vascular risk factors. Parkinsonism & Related Disorders. 2016; 26: 29-34.
10. Rektor I, Rektorova I, Kubova D. Vascular parkinsonism - an update. Journal of the Neurological Sciences. 2006; 248: 185-191.
11. van Zagten M, Lodder J, Kessels F. Gait disorder and parkinsonian signs in patients with stroke related to small deep infarcts and white matter lesions. Movement Disorders. 1998; 13: 89-95.
12. Finsterwalder S, Wuehr M, Gesierich B, Dietze A, Konieczny MJ, Schmidt R, et al. Minor gait impairment despite white matter damage in pure small vessel disease. Ann Clin Transl Neurol. 2019; 6: 2026-2036.
13. Ma R, Zhào H, Wei W, Liu Y, Huang Y. Gait characteristics under single-/dual-task walking conditions in elderly patients with cerebral small vessel disease: Analysis of gait variability, gait asymmetry and bilateral coordination of gait. Gait Posture. 2021; 92: 65-70.
14. van de Schraaf SAJ, Rhodius-Meester HFM, Aben L, Sizoo EM, Peters MJL, Trappenburg MC, et al. Slowing: A Vascular Geriatric Syndrome? J Am Med Dir Assoc. 2022; 23: 47-53 e2.
15. Cai M, Jacob MA, Norris DG, Duering M, de Leeuw FE, Tuladhar AM. Cognition mediates the relation between structural network efficiency and gait in small vessel disease. Neuroimage Clin. 2021; 30: 102667.
16. de Laat KF, Reid AT, Grim DC, Evans AC, Kötter R, van Norden AG, et al. Cortical thickness is associated with gait disturbances in cerebral small vessel disease. Neuroimage. 2012; 59: 1478-1484.
17. Kim YJ, Kwon HK, Lee JM, Cho H, Kim HJ, Park HK, et al. Gray and white matter changes linking cerebral small vessel disease to gait disturbances. Neurology. 2016; 86: 1199-1207.
18. Iseki K, Hanakawa T, Hashikawa K, Tomimoto H, Nankaku M, Yamauchi H, et al. Gait disturbance associated with white matter changes: a gait analysis and blood flow study. Neuroimage. 2010; 49: 1659-1666.
19. Karim HT, Rosso A, Aizenstein HJ, Bohnen NI, Studenski S, Rosano C. Resting state connectivity within the basal ganglia and gait speed in older adults with cerebral small vessel disease and locomotor risk factors. Neuroimage Clin. 2020; 28: 102401.
20. Kim SH, Park JS, Ahn HJ, Seo SW, Lee JM, Kim ST, et al. Voxel-based analysis of diffusion tensor imaging in patients with subcortical vascular cognitive impairment: correlates with cognitive and motor deficits. J Neuroimaging. 2011; 21: 317-324.
21. Koblinsky ND, Atwi S, Cohen E, Anderson ND, Greenwood CE, MacIntosh BJ, et al. Lower Thalamic Blood Flow Is Associated with Slower Stride Velocity in Older Adults. Front Aging Neurosci. 2020; 12: 571074.
22. Su N, Liang X, Zhai FF, Zhou LX, Ni J, Yao M, et al. The consequence of cerebral small vessel disease: Linking brain atrophy to motor impairment in the elderly. Hum Brain Mapp. 2018; 39: 4452-4461.
23. Chen H, Zhang M, Liu G, Wang X, Wang Z, Ma H, et al. Effect of small vessel disease burden and lacunes on gait/posture impairment in Parkinson's disease. Neurol Sci. 2020; 41: 3617-3624.
24. Wan Y, Hu W, Gan J, Song L, Wu N, Chen Y, et al. Exploring the association between Cerebral small-vessel diseases and motor symptoms in Parkinson's disease. Brain Behav. 2019; 9: e01219.
25. Heiland EG, Welmer AK, Kalpouzos G, Laveskog A, Wang R, Qiu C. Cerebral small vessel disease, cardiovascular risk factors, and future walking speed in old age: a population-based cohort study. BMC Neurol. 2021; 21: 496.
26. Charlton RA, Schiavone F, Barrick TR, Morris RG, Markus HS. Diffusion tensor imaging detects age related white matter change over a 2year follow-up which is associated with working memory decline. J Neurol Neurosurg Psychiatry. 2010; 81: 13-19.
27. van der Holst HM, Tuladhar AM, Zerbi V, van Uden IWM, de Laat KF, van Leijsen EMC, et al. White matter changes and gait decline in cerebral small vessel disease. Neuroimage Clin. 2018; 17: 731-738.
28. Pavlović AM, Pekmezović T, Jovanović Z, Medjedović TS, Veselinović N, Norton MC, et al. Transcranial Parenchymal Sonographic Findings in Patients with Cerebral Small Vessel Disease: A Preliminary Study. J Ultrasound Med. 2015; 34: 1853-1859.
29. Schreiber S, Wilisch-Neumann A, Schreiber F, Assmann A, Scheumann V, Perosa V, et al. Invited Review: The spectrum of age-related small vessel diseases: potential overlap and interactions of amyloid and nonamyloid vasculopathies. Neuropathol Appl Neurobiol. 2020; 46: 219-239.
30. Thrippleton MJ, Backes WH, Sourbron S, Ingrisch M, van Osch MJP, Dichgans M, et al. Quantifying blood-brain barrier leakage in small vessel disease: Review and consensus recommendations. Alzheimers Dement. 2019; 15: 840-858.
31. Forsberg KME, Zhang Y, Reiners J, Ander M, Niedermayer A, Fang L, et al. Endothelial damage, vascular bagging and remodeling of the microvascular bed in human microangiopathy with deep white matter lesions. Acta Neuropathol Commun. 2018; 6: 128.
32. Ikram MK, De Jong FJ, Van Dijk EJ, Prins ND, Hofman A, Breteler MM, et al. Retinal vessel diameters and cerebral small vessel disease: the Rotterdam Scan Study. Brain. 2006; 129: 182-188.
33. Kwa VIH, van der Sande J, Stam J, Tijmes N, Vrooland JL. Retinal arterial changes correlate with cerebral small-vessel disease. Neurology. 2002; 59: 1536-1540.
34. Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. Jama. 2002; 288: 67-74.
35. Abdelhak A, Huss A, Brück A, Sebert U, Mayer B, Müller HP, et al. Optical coherence tomography-based assessment of retinal vascular pathology in cerebral small vessel disease. Neurol Res Pract. 2020; 2: 13.
36. Smith EE, O'Donnell M, Dagenais G, Lear SA, Wielgosz A, Sharma M, et al. Early cerebral small vessel disease and brain volume, cognition, and gait. Ann Neurol. 2015; 77: 251-261.
37. Pinter D, Ritchie SJ, Gattringer T, Bastin ME, Hernández M, Corley J, et al. Predictors of gait speed and its change over three years in community-dwelling older people. Aging (Albany NY). 2018; 10: 144-153.
38. Choi P, Ren M, Phan TG, Callisaya M, Ly JV, Beare R, et al. Silent infarcts and cerebral microbleeds modify the associations of white matter lesions with gait and postural stability: population-based study. Stroke. 2012; 43: 1505-1510.

39. Kubota M, Iijima M, Shirai Y, Toi S, Kitagawa K. Association Between Cerebral Small Vessel Disease and Central Motor Conduction Time in Patients with Vascular Risk. J Stroke Cerebrovasc Dis. 2019; 28: 2343-2350.

40. Laveskog A, Wang R, Bronge L, Wahlund LO, Qiu C. Perivascular Spaces in Old Age: Assessment, Distribution, and Correlation with White Matter Hyperintensities. AJNR Am J Neuroradiol. 2018; 39: 70-76.

41. Hu HY, Ou YN, Shen XN, Qu Y, Ma YH, Wang ZT, et al. White matter hyperintensities and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 36 prospective studies. Neuroscience and Biobehavioral Reviews. 2021; 120: 16-27.

42. Stijntjes M, de Craen AJ, van der Grond J, Meskers CG, Slagboom PE, Maier AB. Cerebral Microbleeds and Lacunar Infarcts Are Associated with Walking Speed Independent of Cognitive Performance in Middle-Aged to Older Adults. Gerontology. 2016; 62: 500-507.