The clinical manifestations and pathophysiology of cerebral small vessel disease

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Abstract: Small vessel disease (SVD) is responsible for brain chronic circular disorder, and accounts for 20%–30% cases of ischemic stroke as well as cerebral hemorrhage, and to a great extent, encephalopathy. Binswanger's disease and multiple small strokes, which are common in older people, are also closely associated with SVD. These disorders often cause decline in cognition, vascular dementia, impairment in gait and balance, mood depression, and urinary incontinence, and often brings great social and economic burdens. SVD-related encephalopathy increases the incidences of fall, disability and death in elderly people. With the aging of the society, more attention should be paid to the importance of early diagnosis and prophylactic treatment of SVD. Here the clinical manifestations and pathophysiology of SVD are reviewed.

Keywords: vascular dementia; gait disorder; urinary incontinence; lacunar infarction; Binswanger's disease; brain ischemia; blood brain barrier.

1 Introduction

Cerebral small vessel disease (SVD) is one of the most common causes of cerebrovascular disease. It causes lacunar infarcts, micro-bleeding, and progressive damage to the deep white matter, thus decreasing the life qualities of patients. Cerebral SVD mainly affects the long penetrating arteries (diameter between 30–300 μ m or below 300 μ m) deep within the brain parenchyma with few or no collateral channels. Although the pathogenesis of SVD remains still unclear, some causative factors of SVD have been revealed, including microembolic injuries, hypoperfusion/ischemic injury, blood vessel damage such as lipohyalinosis, fibrinoid degeneration and amyloid angiopathy^[1,2], and metabolism

disorder such as reduction in N-acetylaspartate (NAA), all of which indicate neuron injury^[3]. Binswanger's disease and multiple small strokes are common in the elderly population. With the aging of the society, the importance of early diagnosis and prophylactic treatment of SVD should be greatly noticed.

2 The imaging features of SVD

Since T2-weighted and fluid-attenuated inversion recovery (FLAIR)-magnetic resonance images (MRIs) are more sensitive than CT scanning^[4], visualization of white matter lesions (WML) on cerebral T2-MRIs and FLAIR-MRIs has revealed periventricular hyperintensities (PVHs) and deep white matter hyperintensities (WMHs), while visualization on T1-weighted MRI or CT scanning demonstrates hypointensities. Observations of lacunar infarctions on T2 sequences show deep parenchyma hyperintensities, while observation on T1 sequences show hypointensities. Lacu-

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nar infarctions, which are no more than 15 mm in diameter (3-15 mm), are present in the putamen and caudate nuclei, thalamus, basis pontis, internal capsule, and convolutional white matter, in a descending frequency. CT scanning have shown that the lesions are present in approximately 2/3 ischemic stroke cases, while MRI has detected them in a higher proportion. Black dots in the brain parenchyma visualized on T2*-weighted MRI are just the hemoglobin degradation products^[5]. The number of cerebral microbleeds (CMBs) detected depends on MRI characteristics, such as pulse sequence, sequence parameters, spatial resolution, magnetic field strength, and image post-processing, indicating the importance of MRI in interpreting the results^[6]. MR-Pathological studies of leukoaraiaosis in old people and patients with dementia have revealed arteriolar tortuosity, reduced vessel density, and occlusive venous collagenosis^[7]. At 1.5 T, only large brain arteries can be imaged, thus, the intraarterial digital subtraction angiography (DSA) remains an indispensable tool for investigating medium and small brain artery stenoses^[8]. The noninvasive depiction of the lenticulostriate arteries (LSAs) with three-dimensional time-of-flight MR angiography at 7.0 T can help further understand the pathophysiology of lacunar infarcts that are thought to be caused by SVD^[9].

3 The clinical manifestations of SVD

3.1 Lacunar syndrome Lacunar infarcts are small subcortical infarcts resulting from occlusion of a single penetrating artery. They account for approximately 1/4 of ischemic stroke cases. However, whether lacunes could induce symptoms depends entirely on their locations. In post-mortem studies of a series of 1042 consecutive adult brains, one or more lacunes are detected in 11% cases. Some more frequent symptoms, such as pure motor hemiplegia, dysarthria, pure hemisensory defect, and ipsilateral paresis of conjugate infarcts, are suggested to be the most common causes of pseudobulbar palsy^[10]. Studies in acute ischemic stroke patients undergoing computed tomographic angiography (CTA) also reveal that the majority (44.64%) of stroke cases are attributed to SVD. Rest cases are attributed secondary to atheroembolism (26.79%),

cardioembolism (16.07%) or to an unclear etiology (12.5%)^[1]. Patients with lacunar syndrome mainly exhibit mild or pure symptoms and signs. Recent studies have shown that the prognosis after lacunar infarcts is not benign. Besides, the risk of recurrent stroke is not lower than those of other ischemic stroke subtypes, and there are increased risks of cognitive decline, dementia and death in the long-term. Furthermore, silent SVD has significant prognostic implications, indicating the attack of overt stroke^[11]. Lacunar infarctions are caused by small vessel thrombosis and microemboli. Microemboli occurs frequently in patients with asymptomatic carotid atherosclerosis^[12]. Cerebral microbleeds, asymptomatic or showing mild symptoms, are prevalent in 5.7% (ranging 3.7%-7.7%) of a healthy population, which increases with age. Besides, cerebral micro-bleeds have been observed in 47%-80% of the primary intracerebral hemorrhage patients and in 0-78% of the patients with ischemic cerebrovascular disease^[59]. These findings suggest that CMBs may be a general marker of various types of bleeding-prone SVD and a predictor of recurrent vascular events^[5].

3.2 Vascular cognitive impairment Vascular dementia (VAD) is a term used to describe a heterogeneous groups of diseases, including large vessel disease (LVD) with strategic single and multiple strokes, and SVD such as lacunar state and Binswanger's disease. VAD is the second most common type of dementia, and SVD is one of the most frequent etiologies of VAD (74% of SVD, 18% of LVD, and 8% of both)^[13]. Cognitive dysfunction is suggested to be an early and reliable predictor of chronic cerebral vascular disorder in patients with arterial hypertension. Patients with lacunar state or Binswanger's disease exhibit dementia syndromes with characteristics of subcortical dementia, including slowing of information processing, memory impairment (poor retrieval), poor sustained attention, and executive dysfunction (including poor word list generation and verbal fluency, impaired motor programming with perseveration and impersistence)^[14-16]. Progression of subcortical WMH volume is associated with the decreased performance in the Logical Memory Testing^[17]. Postmortem studies in 30 cases of VAD have revealed that both lacunes and diffuse softening are predominant in the frontal lobes^[18], which probably

results from ischemic interruption in parallel circuits from the prefrontal cortex to the basal ganglia and in the corresponding thalamocortical connections.

3.3 Gait disorder Gait disorder is common in older patients, and the incidental fall may have harmful effects on them. In the healthy elderly, the lower score on the Digit Symbol Substitution Test (DSST) and slower gait are associated with greater risks of mortality and developing incident disability independent of other risk factors^[19]. The Sydney Older Persons Study examined 6-year outcomes of 630 community-dwelling participants aged 75 or over. Results have shown that those with cognitive impairment in combination with gait and motor slowing are the most likely to dement over the 6-year period, most likely to die. Simple measures of gait may provide useful clinical tools, facilitating the prediction of dementia^[20].

The main clinical manifestations of gait disorder include slower gait, shorter stride length and longer double support times, and gait apraxia (characterized primarily by gait ignition failure, akinetic mutism, and rigidity)^[21]. In Parkinson's disease (PD) patients, age-related brain change may contribute to axial features^[22]. In multiple lacunar state patients, gait and speech disturbances are the most frequent initial symptoms, followed by slow motion. Increasing baseline WML volume is closely associated with any incidental fall or multiple incidental falls. The risk of incidental fall doubles in the 20% patients with highest lesion volumes, compared with the lowest. The effect of WML volume on the risk of falls is magnified in people with poor quadriceps muscle strength and a greater gait variability^[23-25].

Disconnection, or dysfunction of supplementary motor area (SMA) may account for gait disorder observed in patients with Binswanger's disease, hydrocephalus, frontal lobe lesions, and PD. Parasagittal convexity premotor cortex plays a role in the genesis of gait apraxia^[26]. Tc-99m HMPAO brain SPECT imaging shows bilateral mediofrontal hypoactivity^[27]. In normal subjects, white matter signal abnormality (WMSA) volume increased by $(0.02 \pm 0.05)\%$ intracranial cavity volume (ICCV) per year, while in mobility impaired subjects, WMSA increased 5 times faster, $(0.10 \pm 0.10)\%$ ICCV per year. This suggests that subjects with mobility impairment have

accelerated, disease-related WMSA accrual^[28].

The concept of vascular parkinsonism (VP) ("atypical parkinsonism" and "pseudo-parkinsonism") has been highly controversial since the initial report by Critchley in 1929. The age of PD onset is (55 ± 12) years while the age of VP onset is (62 ± 13) years. Most often, VP is atypical on the basis of the presence of additional focal signs, and the absence of typical resting tremor in the upper limbs, true akinesia (i. e., with decrement and fatiguing of alternating movements), and the definite benefit from levodopa. Importantly, the rigidity is paratonic, and tremor is action or postural. Besides, the lesions responsible for VP are mostly basal ganglia lacunes and/or subcortical white matter vasculopathy of the "Binswanger" type. On the contrast, the single striatal infarct, striatal cribriform cavities or ischemic changes in the substantia nigra have been rarely described. Vascular "pseudo-parkinsonism" refers to isolated gait disorders called "lower body parkinsonism", "frontal-type gait disorders" or "gait ignition failure" that are distinct from Idiopathic PD (IPD)^[29,30].

Freezing of gait (FOG), commonly seen in advanced PD, is actually more common in atypical parkinsonism, including VP. Approximately 50% of atypical parkinsonism patients have FOG^[31,32]. Most patients exhibit bilateral bradykinesia and rigidity, characterized predominantly by a shuffling gait^[33,34].

3.4 Incontinence and depression Leukoaraiosis is also associated with depressive symptoms and urinary incontinence. WMLs are associated with substantial disabilities and should not be considered as a benign and silent condition. Measures against vascular risk factors should be taken in early life or midlife in order to prevent WMLs-associated functional impairment^[35]. WMH volume is significantly associated with urinary incontinence, grasp reflex, and aberrant motor behaviors^[36]. Frontal bladder control (urge incontinence and nocturia) should improve the determination of functional status and disability, and more accurately measure the effects of potential therapies^[37].

Among patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), 41% are apathetic. Apathy is associated with a higher load of white matter and lacunar lesions, lower scores of Mini-Mental State Examination (MMSE) and Mattis De-

mentia Rating Scale (MDRS), and more global disability. Patients are more limited in Instrumental Activities of Daily Living (IADL)^[38,39]. Apathy is ubiquitous in VAD patients. Depression and psychosis are also common. Poststroke depression (PSD) (3 months after stroke) is more frequent in patients with large artery disease than in SVD patients, suggesting that cerebral blood perfusion may play an important role in the development of PSD.

4 The pathophysiology of SVD

4.1 Metabolic and blood brain barrier (BBB) changes caused by heterogeneous etiology Binswanger's disease is associated with demyelination in extensive regions and the presence of inflammatory cells around damaged blood vessels. Microembolism and microthrombosis can initiate inflammation, causing BBB disruption and organ dysfunction. In a recent report, 60-100 nm cholesterol crystals were injected into young and middle-aged rats via bilateral internal carotid artery at an interval of 2 weeks. After 24 h, matrix metalloproteinase activation is detected in 50% of the animals. Meanwhile, perivascular albumin staining is detected at 4 d, but rarely persists beyond 1 week. Activations of microglia and astrocytes also occur in all the animals and persist for up to 8 weeks, and inflammatory areas are small and scattered^[11]. Moreover, cerebral SVDs, including lacunar stroke and confluent leukoencephalopathy, also exhibit a reduction in the level of NAA, a marker of neuronal integrity^[3].

4.2 Hypoperfusion/ischemic injury Previous reports have indicated that the regional cerebral blood flow (rCBF) in the SVD group is significantly decreased in the WML patients, and the white matter severity is associated with subcortical and average white matter CBF, as revealed by both brain perfusion single-photon emission computed tomography (SPECT) and CT perfusion (CTP)^[40,41].

In a mouse model of chronic cerebral hypoperfusion, WMLs are successfully induced^[42] through bilateral common carotid artery stenosis using external microcoils with varying inner diameters. Chronic ischemia in frontal white matter could interrupt frontal-cerebellar circuits, induce hypometabolism in cerebellar regions, and decrease perfusion

and apparent diffusion coefficient (ADC)^[43].

4.3 Risk factors for small vessel damage

4.3.1 Genes Meta-analysis of the genetic effects on different subtypes of SVD stroke and LVD stroke have been conducted widely. From the initial search of 526 manuscripts, 5 candidate genes, including ACE/DD, eNOS intron 4 a/b, MTHFR C677T, ApoE/epsilon4 and PAI-A 4G/5G, are studied in 7533 cases (LVD 4180, SVD 3352) and 9835 control subjects. There is a preferential association for SVD, rather than LVD, with ACE/DD and eNOS intron 4 a/b, polymorphism, although the statistical significance is not reached. Meanwhile, no such preference is observed for MTHFR C677T, ApoE/epsilon4 or PAI-A 4G/5G polymorphism^[44]. Analysis of haptoglobin (Hp) 2-2 phenotype in a group of patients with first symptomatic lacunar stroke has revealed that Hp1 allele frequency is significantly higher than that in control group, mainly due to a lower Hp2-2 phenotype frequency. This discrepancy is more significant in younger (≤ 60 years) patients. The association between Hp1 and lacunar stroke may relate to BBB dysfunction, or a special dependence of small vessel wall integrity on Hp2-2 related angiogenic potential^[13]. Besides, the coagulation factor XIII subunit B gene (F13B) His95Arg variant is more common in LVD patients than in SVD patients, and none of the 21 other prothrombotic gene variants are associated with LVD or SVD^[45].

CADSIL is an autosomal dominant condition, resulting from mutation of *Notch3* gene that is located on chromosome 19. Postmortem examination has revealed a Binswanger type of leukoencephalopathy caused by a peculiar microangiopathy^[57]. Microangiopathy has shown a slight basophilic small arterial granular degeneration of the medial sheath associated with the presence of ballooned smooth muscle cells with clear cytoplasm, in a large Italian kindred in which an autosomal dominant late-onset leukoencephalopathy occurs^[58]. Electron microscopic study reveals degenerative changes in the parietal vessels with notable increases of basal-membrane-type material and electron-dense granular deposits. Eosinophilic and non-amyloid material of undetermined origin has also been detected close to the smooth muscle cells^[46].

4.3.2 Other risk factors Asymmetric dimethylarginine

(ADMA) is an indicator of endothelial dysfunction. Recently, it has been demonstrated as a new independent risk factor for adverse cerebrovascular events in SVD, while conversely, *L*-arginine (*L*-Arg) may play a protective role. In CADASIL patients, the plasma level of ADMA is significantly higher than that in control subjects^[47]. In patients with vascular parkinsonism, anticardiolipin antibodies (ACLA) have been obtained in 40-50% patients^[48].

Hypertension that occurs in a kindred, can cause injuries to the vasculature, even before the diagnosis of hypertension. Hypertension is the most important risk factor for SVD^[49]. In patients with a family history of hypertension, the vasculature has already been damaged before the onset of high blood pressure. There is a gradual increase in blood pressure and an early change in arterial elasticity in young healthy individuals. A study concerning large arterial compliance (C1) and small arterial compliance (C2) has been conducted in young normotensive individuals, aged 16-30 years. Results suggest that men with at least one hypertensive parent, have lower C1 and C2 levels, together with higher systolic blood pressure (SBP) and diastolic blood pressure (DBP). Those with only hypertensive grandparents have intermediate C1, C2 and blood pressure levels. There is a linear relationship between C1 and SBP or DBP^[50].

Homocysteine is an endothelial toxin and the elevation of its level has been indicated as a risk factor of stroke. In white population, elevated homocysteine level is associated with SVD, especially confluent leukoaraiosis, probably through endothelial dysfunction, suggesting that homocysteine correlates with leukoaraiosis severity^[51].

Diabetes mellitus can lead to alterations in BBB structure^[52]. Addition of a high-fat diet in type 2 diabetic patients will exacerbate small artery remodeling and compliance. Vascular remodeling indices [(media to lumen ratio, M/L), collagen abundance and turnover, and matrix metalloproteinase (MMP) dynamics], mechanical properties (vessel stiffness) and reactivity to pressure and vasoactive factors, would be damaged by diabetes. Another study shows that addition of a high-fat diet to type 2 diabetic Goto-Kakizaki rats could increase constriction in response to endothelin-1, and in-

duce impairment in vasorelaxation in response to both acetylcholine and sodium nitroprusside^[53].

Cerebrovascular WMLs are accompanied by oligodendroglia apoptosis. Immunohistochemistry analysis has shown that DNA fragmentation occurs in glia cells and caspase-3 level is up-regulated in the oligodendroglia of the white matter. These results demonstrate that chronic cerebral hypoperfusion induces white matter degeneration in association with DNA fragmentation in oligodendroglia^[54].

Amyloid angiopathy is associated with Alzheimer's disease (AD) and causes stroke which, even small, can still lower the threshold for dementia when co-existing with AD. Apolipoprotein E (apoE) plays a role in the pathogenesis of AD. It is involved in receptor-mediated cellular clearance of amyloid beta protein (A β) and in the perivascular drainage of extracellular fluid. In blood vessels, apoE and immunoglobulin G are detected within the SVD-altered vessel wall. The severity of SVD is associated with the occurrence of apoE in the vessel wall and A β in perivascular astrocytes, suggesting that the presence of SVD results in plasmaprotein leakage into the brain^[55]. Widespread A β deposition disregulates basement membrane of the capillaries, leading to the disturbance of the microcirculation throughout the cerebral cortex, without obvious ischemic disintegration of the neuropil^[56].

5 Conclusion

To sum up, the vasculature can be damaged due to various etiologies, leading to BBB injury, inflammation, vascular tortuosity, brain hypofusion/ischemia, apoptosis of glia and neurons, *etc.* Vascular risk factors damage the small vessel through different mechanisms. Manifestations of lacunes and leukoaraiosis which result from cerebral SVD, include cognitive decline or dementia, gait difficulties, urinary incontinence, parkinsonian symptoms, pseudobulbar palsy, and emotional incontinence. Interventions in the vascular risk factors should be conducted in early life or mid-life to prevent the functional impairment associated with SVD in old age.

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脑小血管病的临床特点及病理生理机制

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摘要: 小血管病与慢性脑循环障碍相关, 占缺血性卒中的 20%-30%, 也是大部分脑出血和脑病的病因所在。与小血管病相关的疾病包括 Binswanger 病、多发小灶中风和微出血, 这些疾病在老年人中的发病率极高, 且往往导致认知减退或血管性痴呆、步态和平衡障碍、情绪低落、尿失禁等。小血管病相关性脑病预示着老年人跌倒、致残和死亡的几率增加, 因此其临床特点和病理生理机制正日益受到关注。本文对脑小血管病的危险因素、发病机制、病理以及临床表现作一综述。

关键词: 血管性痴呆; 步态障碍; 尿失禁; 腔隙梗死; Binswanger 病; 脑缺血; 血脑屏障