Review paper

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Review of neuroimaging research progress of cerebral small vessel disease

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Abstract

Cerebral small vessel disease (cSVD) is a disease defined by clinical symptoms and neuroimaging, which often causes a series of pathophysiological changes, blood-brain barrier destruction, brain tissue ischemia and involves cerebral arterioles, capillaries and venules. The exact pathogenesis of cSVD is unclear and there is no specific prevention and treatment for this potentially high disability rate disease.

This article reviewed the latest research progress of neuroimaging of cSVD in order to improve our understanding of cSVD's manifestation and potential mechanism.

We introduced the neuroimaging markers which can be accurately identified by diffusion tensor imaging, including recent subcortical infarction, white matter lesions, brain atrophy, lacunar infarction, cerebral microhaemorrhage and other cSVD neuroimaging markers. Besides, we also interpreted the total load score of cSVD, which described a wide range of clinical, pathological and neuroimaging features, reflecting the acute and chronic damage of the whole brain.

Combined with the neuroimaging methods, capturing the imaging features of early cSVD can improve the diagnostic ability of cSVD and provide strong support for the longitudinal study.

Key words: *cerebral small vessel disease, imaging, research progress.*

Introduction

Cerebral small vessel disease (cSVD) is characterized by a series of clinical, imaging and pathological changes caused by various causes, including cerebral arterioles, arterioles, capillaries and venules [18]. The main clinical manifestations of cSVD are stroke attack, mild cognitive impairment, unstable gait or asymptomatic [33]. At present, the diagnosis of cSVD mainly depends on magnetic resonance imaging (MRI). MRI signs are critical for the diagnosis of cSVD and the assessment of its progression. Recent studies have shown that the cognitive decline can be predicted by the combination of physical signs and the overall burden of cSVD. At the same time, patients with cSVD show some differences in the disease progression and brain damage, which can be explained by the heterogeneity of the disease and its pathogenesis. The main traditional imaging markers are recent small subcortical infarction, lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), brain atrophy and so on [7]. Due to the development of new magnetic resonance technology, cerebral microbleeds (CMBs), resting cerebral blood flow (CBF), cerebrovascular reactive (CVR), morphology of arterioles and veins are also used as new imaging markers [31].

This article will review the relevant researches of cSVD neuroimaging, in order to improve the understanding of cSVD's manifestation and potential mechanism, and provide strong support for the diagnosis of cSVD.

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Material and methods

We firstly reviewed the paper which reported the cSVD neuroimaging markers and raised the concept of total load score of cSVD, then according to the researches about the previous eight models of CSVD total load score, we searched and studied the related papers in 'PubMed' and combined studying the articles and guidelines for Neurovascular Units. We controlled the quality of studies cited in this paper according to the impact factor and times cited.

Neurovascular unit

Cerebrovascular disease is an important risk factor for vascular cognitive impairment, dementia and other functional decline in the elderly without stroke [23]. In the past, cerebral vessels and brain cells were regarded as two different entities, and a strict distinction was made between cerebral blood diseases and neurodegenerative diseases, but more and more studies have shown that they were closely related, and this interaction is gradually conceptualized as neurovascular unit (NVU) [29].

Neurovascular unit is mainly composed of endothelial cells (EC), smooth muscle cells (SMC), basement membrane (BM), perivascular space (Virchow-Robin), pia mater and astrocytes. As the blood vessels go deep into the brain, SMC and the meningeal covering layer disappear, while NVU increases between EC and astrocytes [22,37]. At present, endothelial cell dysfunction has been considered to be an important mechanism of cSVD, which can lead to autoregulation, impaired vascular reactivity [35]. Cerebral vascular matrix is a key component of NVU, which is very important for the normal operation of NVU [12]. The structural and functional integrity of NVU plays a vital role in overall brain health. Damage to any NVU composition will lead to chronic deterioration of cerebrovascular disease, which inevitably leads to cognitive impairment, dementia, increased risk of stroke, etc. [28]. So far, although a large number of studies have been carried out to crack the structure and function of NVU, the mechanism and therapy of cSVD have not been greatly developed due to the difficulty in observing cerebral microvessels in biochemical and physiological studies and the lack of appropriate animal models [3].

Previous neuroimaging of cerebral small vessel disease

The diagnosis of cSVD mainly depends on neurostructural imaging. MRI sequences usually include T1-weighted magnetic resonance imaging (T1WI), T2-weighted magnetic resonance imaging (T2WI), T2 fluid attenuated inversion recovery (T2-FLAIR), diffusion weighted imaging (DWI) and susceptibility weighted imaging (SWI). Diffusion Tensor imaging (DTI) can accurately identify recent subcortical infarction, white matter lesions, brain atrophy, lacunar infarction, cerebral microhaemorrhage and other cSVD neuroimaging markers. Besides, each sequence reflects specific tissue characteristics [11].

Recent subcortical small infarction

Recent subcortical small infarction occurs in the perfusion area that penetrates the arterioles within the brain. About 25% of acute ischemic stroke is caused by recent subcortical small infarction. MRI showed low signal intensity of T1WI, high signal intensity of T2WI and T2-FLAIR. In addition to evolving into lacunar foci, it can also be transformed into non-cavitary outcomes, such as high signal intensity of white matter and disappearance of infarcts [16]. Recent subcortical small infarcts can be up to 15-20 mm in diameter [34].

Lacunae

Lacunae can be found in asymptomatic elderly patients with round cerebrospinal fluid signal lesions of 3-15 mm in diameter; whether symptomatic or asymptomatic, most lacunae are considered to be small subcortical infarctions; but some may be caused by small deep haemorrhage. A large number of studies have found that lacunae are an important predictor of cognitive impairment in patients with cSVD [4].

High signal in white matter

On T2-weighted MRI, white matter lesions characterized by bilateral and mostly symmetrical high signal intensity are very common in the elderly. WMH in the periventricular area (connecting subcortical and deep white matter) can explain the decrease in processing speed, which is a part of executive dysfunction and is considered to be an iconic cognitive feature of aging. The mechanisms of white matter lesions are complex, including low perfusion and endothelial injury, BBB destruction and permeability changes, white matter cell dysfunction, apoptosis, autophagy and transmitter changes, cytokines, inflammatory response and oxidative stress, abnormal gene expression and brain-gut axis dysfunction [39].

Cerebral microhaemorrhage

Cerebral microhaemorrhage is a small low signal lesion on SWI, which is most common in the cortical-subcortical junction, as well as in the deep grey or white matter of the cerebral hemisphere, brainstem and cerebellum. Emerging data show a link between microhaemorrhage and cognitive impairment. And in the case of strong artery stenosis or occlusion, the cere-

bral arterioles will form collateral pathways, the number of which will increase and twists and turns, and at the same time, it is more likely to bleed.

Virchow-Robin dilatation

Virchow-Robin space is an extension of the extracerebral vascular space, which surrounds arteries, arterioles, veins and venules. The Virchow-Robin space is usually microscopic and invisible in traditional neuroimaging [25]. However, the older you get, the space becomes more and more obvious, especially at the bottom of the brain. In general, the enlargement of Virchow-Robin space is related to other morphological features of cSVD, such as high intensity of white matter and lacunae, but does not include brain atrophy. Whether the existence of Virchow-Robin space has clinical significance is controversial, so it should not be called a lesion [14]. However, some studies have shown that significant Virchow-Robin dilatation has worse cognitive function [40].

Brain atrophy

Brain atrophy usually occurs in the aging process, but the degree varies from individual to individual and can be whole-brain and focal. Pathological studies showed that brain atrophy included neuronal loss, cortical thinning, subcortical vascular stenosis with white matter thinning, arteriosclerosis, venous collagen deposition, and secondary neurodegenerative changes. Many imaging studies have shown that there is a close relationship between the existence and severity of cSVD and brain atrophy [2] (see Fig. 1).

Total load score of cerebral small vessel disease

The total load score of cSVD was first proposed at the European Neuroimaging Conference in 2013, which describes a wide range of clinical, pathological and neuroimaging features, reflecting the acute and chronic damage of the whole brain to NVU [34]. The total load score is quantified according to the imaging markers

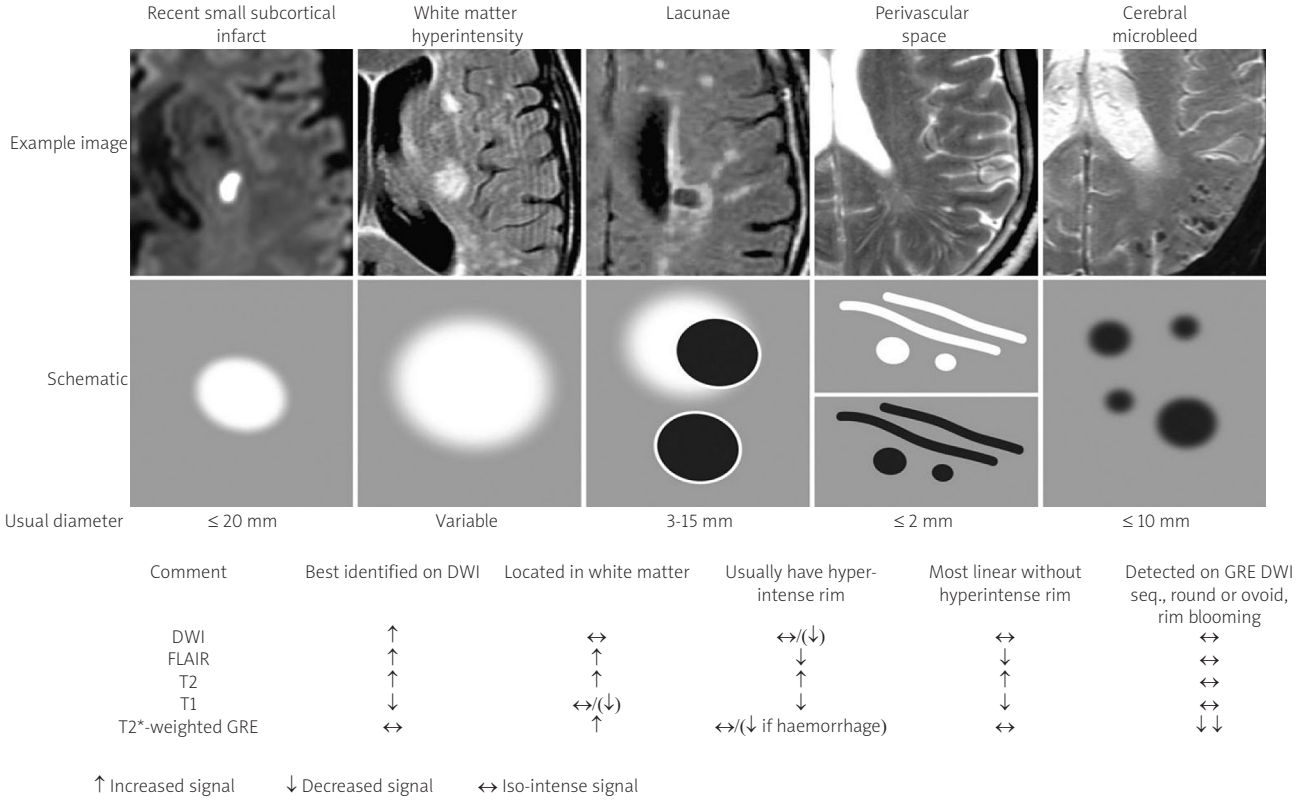

Fig. 1. MRI findings for lesions related to small vessel disease show examples (upper) and schematic representation (middle) of MRI features for changes related to small vessel disease, with a summary of imaging characteristics (lower) for individual lesions. DWI – diffusion-weighted imaging, FLAIR – fluid-attenuated inversion recovery, SWI – susceptibility-weighted imaging, GRE – gradient-recalled echo.

of the whole brain, making it an effective method to evaluate the severity of cerebrovascular disease. More and more people have noticed that the total load score has some advantages over single imaging. At the same time, magnetic resonance multimodal imaging has gradually become the dominant examination mode of imaging, which provides effective technical support for promoting the wide application of total load score.

Yang *et al*. found that 24-hour, diurnal systolic blood pressure level and systolic blood pressure variability were positively correlated with cSVD burden. At the same time, Yang *et al*. found that brachial-ankle pulse velocity (baPWV) is related to acute and chronic cSVD, and also showed that arterial stiffness is related to the pathogenesis of SVD, arterial stiffness can become a therapeutic target for SVD [38]. Riba-Llena *et al*. found that in a group of hypertensive individuals, arterial stiffness was associated with the total load of cSVD, especially with internal capsule and basal ganglia EPVS [26]. Hilal *et al*. found that cSVD is associated with cognitive impairment, and cSVD therapy should be a therapeutic target for delaying the progression of cerebrovascular disease and potential cognitive decline [10]. Wiseman *et al*. found that patients with systemic lupus erythematosus have an increased risk of stroke, and patients with systemic lupus erythematosus have a higher cSVD total load score, mainly characterized by enlarged perivascular space [36]. Lau *et al*. found that the total cSVD score had predictive value for recurrent stroke after transient ischemic attack (TIA)/ischemic stroke. The prediction of recurrence in non-lacunar patients highlights the potential role of cSVD in the broader aetiology of stroke [15]. Song *et al*. found that patients with atherosclerosis had a higher SVD score, and there was a positive correlation between systemic atherosclerosis and SVD score in patients with acute ischemic stroke [32]. Arba *et al*. found that cSVD has an effect on the outcome of stroke after intravenous thrombolysis, and white matter lesions are the main driving factors for the aggravation of the disease [1]. Liu *et al*. evaluated the correlation between total load score and bleeding transformation and 90-day prognosis after intravenous thrombolytic therapy in acute stroke. The results showed that total load score was not only a predictor of venous thrombolytic bleeding transformation, but also an independent risk factor for 90-day poor prognosis (OR = 3.157, 95% CI: 2.120~4.703). cSVD overall load score ≥ 2 can be used as an imaging predictor of poor short-term neurological prognosis after rt-PA treatment for acute ischemic stroke [15,19] (Table I).

New imaging markers of cerebral small vessel disease

With the development of new magnetic resonance technology, some new markers have been found, which can measure the integrity of the vascular system more directly and deepen our understanding of cSVD.

The morphological characteristics of arterioles and veins (curvature, density)

Usually, the small perforating arteries of the white matter and basal ganglia and venules in the periven-

Table I. Summary of review articles

Author [Ref.]	Theme
Neuroimaging of cSVD	
Lee *et al.* [16]; Wardlaw *et al.* [35]	Recent subcortical small infarction
Benjamin *et al.* [4]	Lacunae
Zhai *et al.* [39]	High signal in white matter
Pollock *et al.* [25]; Kwee *et al.* [14]; Zhu *et al.* [40]	Virchow-Robin dilatation
Aribisala *et al.* [2]	Brain atrophy
Total load score of cSVD	
Yang *et al.* [38]; Riba-Llena *et al.* [26]; Song *et al.* [32]	Arterial stiffness is related to the pathogenesis of SVD
Hilal *et al.* [10]	cSVD is associated with cognitive impairment
Wiseman *et al.* [36]	Systemic lupus erythematosus have a higher cSVD total load score
Lau *et al.* [15]; Liu *et al.* [19]	Total cSVD score had predictive value for recurrent stroke after TIA/ischemic stroke
Arba *et al.* [1]	cSVD has an effect on the outcome of stroke after intravenous thrombolysis
New imaging markers of cSVD	
Seo *et al.* [30]; Kang *et al.* [13]; Bullitt *et al.* [6]	The morphological characteristics of arterioles and veins (curvature, density)
Brown *et al.* [5]; Pettersen *et al.* [24]; Riddle *et al.* [27]; Hainsworth *et al.* [9]	Cerebral blood flow (CBF) and vascular reactive (CVR)

tricular area are lower than the resolution of most non-invasive techniques (CT and MRI), so it is difficult to observe. But these penetrating arterioles and veins become more obvious through ultra-high field TOF-MRA and contrast media. The cerebral arterioles measured by 7T magnetic resonance angiography showed that patients with subcortical vascular dementia and young patients with hypertension had fewer trunks and branches than the control group. In addition, older patients and patients with subcortical vascular dementia had greater arterial twists at 3 T and 7 T angiography [6,13,30].

In cadaveric specimens with cSVD, small vessels show a curved pencil-like structure with a thick basal layer. The curvature of cerebral arterioles is considered to be a sign of pathology and has been noted in WMH [6,13,30].

At the same time, it is often believed that the injury of small vessels only affects arterioles and capillaries, not including the venous end of microcirculation, but venules are more vulnerable than arterioles. Because of the slow flow and low pressure of the venule blood, it promotes the adhesion of inflammatory cells to the venule endothelium, and the thin wall promotes angioedema to damage the interstitial circulation and cause abnormal Virchow-Robin space.

Cerebral blood flow and vascular reactive

Cerebral blood flow (CBF) measurement methods include positron emission tomography (PET; gold standard), CT perfusion, enhanced nuclear magnetic resonance, arterial spin labelling (ASL) and so on. In the past, people only focused on cortical blood perfusion, ignoring white matter perfusion; there was a significant difference in vascular density between grey matter and white matter, grey matter injury directly affected neurons, and white matter injury mainly affected glial cells which lead to damage or loss of axonal function [5,24]. Executive dysfunction is an iconic cognitive feature of aging, including information processing speed, attention, cognitive flexibility and so on [27]. The WMH in the periventricular area (connecting the subcortical and deep white matter) can explain the decrease in processing speed. Vascular reactivity (CVR) is the regulation of blood flow, each part of NVU has the ability to regulate blood flow, mainly endothelial cells. Endothelial dysfunction has been considered to be an important mechanism of cSVD, and it is considered to be an early sign of cSVD, which appears before obvious radiological signs. The measurement of vascular reactivity is difficult, but the recent combination of hypercapnia and ASL can make the measurement of CVR more accurate [9].

Differences between this article and other reviews

Some reviews on the application of neuroimaging in cSVD have been published [7,8,17,20,21,39]. For example, the review of Caunca *et al*. [7] focused on describing the neuroimaging and age-related cognitive changes of cerebrovascular diseases in the elderly with normal cognition. Gurol *et al*. [20] focused on the contribution of neuroimaging in evaluating the mechanism of common sporadic cSVD in living humans. By reviewing the relevant literature on cSVD, this paper systematically summarized the existing neuroimaging techniques and characteristics of clinical diagnosis of cerebrovascular diseases, which could be used to clarify the possible pathogenesis of cSVD.

Conclusions

To sum up, cSVD can be characterized by acute small vessel stroke, occult cognitive impairment or dementia, gait dysfunction, incontinence, depression in old age or without any clinical symptoms only based on neuroimaging examination. The symptoms are various and the pathological mechanism is complex. Neurovascular unit and total load score are favourable models for explaining cerebrovascular diseases. At the same time, with the development of more advanced structural and functional radiological techniques, the more accurate explanation of cSVD markers on the pathogenesis of the disease is further strengthened. Combined with the neuroimaging methods, capturing the imaging features of early cSVD can improve the diagnostic ability of cSVD and provide strong support for the longitudinal study after the changes of cSVD radiological markers which could elucidate the spatio-temporal evolution of injury and provide clues for the pathogenesis of cSVD.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The Second Affiliated Clinical Medical College of Inner Mongolia University for Nationalities.

Disclosure

The authors report no conflict of interest.

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