

Potential Mechanism of Venous System for Leukoaraiosis: From post-mortem to in vivo Research

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Keywords

Leukoaraiosis · Venous collagenosis · Neuropathology · Susceptibility-weighted imaging

Abstract

Background: Leukoaraiosis (LA), widely accepted as a feature of cerebral small vessel disease, significantly increases the incidence of stroke, dementia, and death. Cerebral small artery disease has been considered as one of the main causes of LA. However, since the term “venous collagenosis” (VC) was proposed in an atrophy research in 1995, there have been pathological and neuroimaging studies proving the association between the venous system and LA in aging, Alzheimer’s disease (AD), and Parkinson’s disease. **Summary:** Autopsy studies confirmed that thickening of the lumen wall in venules, which results from the deposition of collagen I and III, leading to vessel stenosis or occlusion, is closely associated with LA. Susceptibility-weighted imaging research revealed a controversial association of deep medullary veins and LA in vivo, regarding which there are no standard criteria currently. Nevertheless, retinal venous changes had been reported to increase the risk of LA development, providing a

novel way for in vivo evaluation. As for the internal jugular vein, jugular venous reflux could double the LA score in aging and modulate circulation of cerebral spinal fluids. **Key Messages:** Disruption of the venous system was notably associated with LA in aging, AD, and Parkinson’s disease post-mortem and in in vivo models. The venous pathological changes may induce cerebral hypoperfusion, drainage system disruption, and vasogenic oedema in the veins around the periventricular white matter. The clarification of VC in LA may provide an early prevention and early treatment strategy for LA patients.

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Introduction

Leukoaraiosis (LA), also known as white matter changes, white matter hyperintensities, or white matter lesions, is a typical neuroimaging feature of cerebral small vessel disease (CSVD) [1–3]. Bilateral, patchy, or diffuse areas of hypodensity on computed tomography or hyperintensities on T2-weighted magnetic resonance imaging (MRI) scans are the typical imaging findings [4]. Clinical fea-

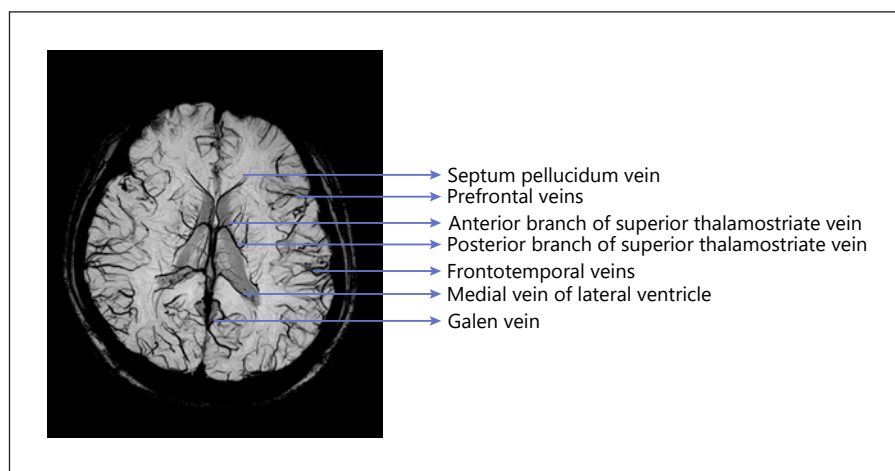


Fig. 1. Superficial veins and deep medullary veins around ventricles on susceptibility-weighted imaging.

tures such as cognitive dysfunction, motor dysfunction, depression, and urinary problems have been associated with LA [5, 6]. Despite the numerous studies on LA and CSVD, the pathological mechanism of LA remains unclear. Currently, the main theories with regard to the pathogenesis of LA focus on endothelial damage, disruption of the blood-brain barrier, and the infiltration of inflammatory factors and cytokines [7–12].

It is generally accepted that white matter is vulnerable to cerebral hypoperfusion because it is supplied by the long medullary arterioles, which arise from the border zone between the middle cerebral and anterior cerebral arteries, lacking a collateral circulation [13]. However, advancements in neuroimaging technology have contributed to our understanding of the venous anatomy in the white matter and have indicated that venous insufficiency may be correlated with LA. The venous system in the brain consists of a superficial and a deep venous system [14]. The superficial venous system collects blood from the cerebral cortex, while the deep venous system collects blood from the parenchyma, including the medulla, basal ganglia, and periventricular area (Fig. 1). These two venous systems drain into the dura sinus, internal jugular vein, and finally the heart. The venous system modulates brain blood flow and cerebral spinal fluid circulation. Imbalance of the venous system may lead to disruption of the blood-brain barrier, infiltration of inflammatory factors, vascular remodelling and pyroptosis.

Venous collagenosis (VC) was first described by Moody et al. in 1995 [15]. In this study, in addition to arteriolar tortuosity, VC, composed of collagen I and III, was observed in the periventricular white matter lesions,

and was named “periventricular venous collagenosis (PVC).” In the following years, neuroimaging studies on PVC and retinal veins have verified that venous changes are closely associated with LA, which may help elucidate possible mechanisms and interventions in patients with LA. In this review, we have provided a complete and updated survey of the venous system in LA.

Neuropathological Studies

Autopsy Studies

VC is characterised by the thickening of the lumen wall in venules, which could lead to vessel stenosis or occlusion. Moody et al. [15] studied 22 subjects without brain disease and evaluated the pathological vascular changes in LA using MRI and histochemical staining after death. They observed that 65% of subjects (13 out of 20 patients) over 60 years old exhibited periventricular venous stenosis; further, 10 patients showed severe PVC accompanied by severe LA. Interestingly, they pointed out that pathological changes of collagenosis in veins could easily be mistaken as hyaline changes of the artery on haematoxylin and eosin staining, which could be the reason why PVC had been overlooked before [15]. They also scored the severity of venous disease based on the narrowing of the lumen due to VC (Fig. 2). In another study on 186 human brains, researchers proposed that arteriole tortuosity and VC may both contribute to LA [16]. It is worth noting that in the study by Moody et al., VC appeared with aging, particularly in the areas of LA, and this is in accordance with the findings related to atrophy research in the aging human brain [17].

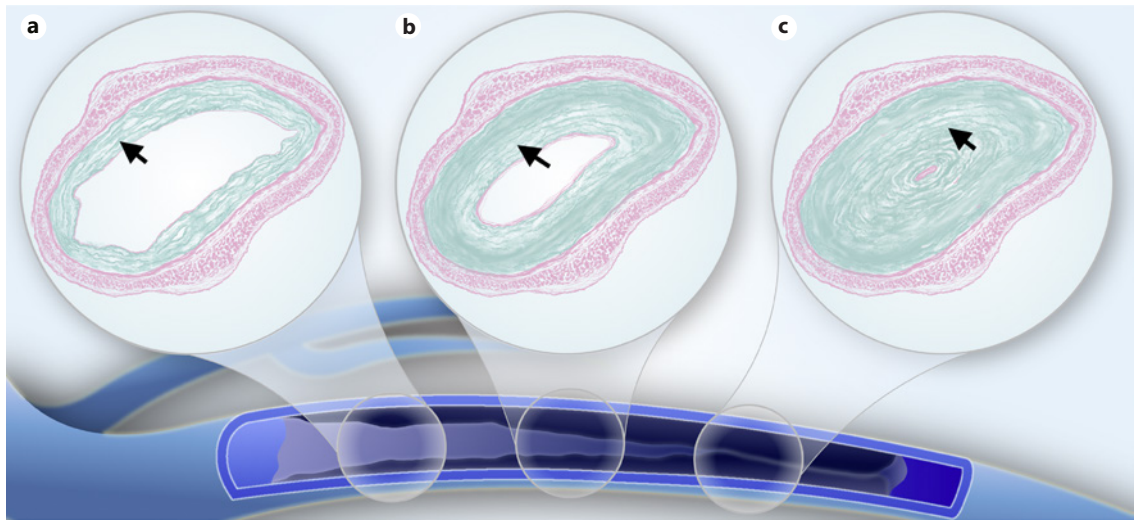


Fig. 2. Grades of venous collagenosis. **a** Lumen occupying at least 75% of the total vessel diameter with thickened walls around it, which consist of venous collagenosis (arrow). **b** Lumen occupying less than 50% of the vessel diameter with thickened walls (arrow). **c** Venous occlusion or severe stenosis by collagenous wall (arrow).

Since research on human brain samples is rare, there was little atrophy research on VC. In 2017, Keith et al. [18] reported their work on LA and VC in patients with Alzheimer's disease (AD) using premortem MRI and histological studies with haematoxylin-eosin and trichrome staining to score LA and stenosis of venules; they observed no significant differences with regard to VC or LA changes between AD and non-AD patients. VC is not a specific pathological change in AD patients. However, when veins were graded by size, the severity of small vein (including capillaries) VC, medium vein VC, and large calibre VC (>200 μm) was significantly greater in the presence of higher LA scores. Stenosis of large calibre veins was the most notable predictor of LA score both in AD and non-AD patients, and this was the first study to confirm this. The possible mechanism of VC leading to LA could be dependent on the rigidity of the larger calibre veins, thus potentially decreasing the venous pulsation and propulsion of perivenous interstitial fluid flow.

Other than AD, LA is also seen in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) disease [19]. Damage to arterioles and LA are the main feature of CADASIL disease. However, Pettersen et al. [20] reported that VC, which is periodic acid-Schiff negative and trichrome positive, could also be seen in patients with CADASIL. Arteriolar changes cause a decrease in perfusion and stimulate the collagen deposition in the venous wall and, thus, re-

sult in VC. Though lacking further evidence, this hypothesis may provide direction for future VC research.

Animal Studies

Hartmann et al. [21] suggested that ex vivo research of deep medullary veins (DMVs) is rare, due to the difficulties in the differentiation of VC and arteriole hyalinisation using haematoxylin-eosin staining. Application of alkaline phosphatase, α -smooth muscle actin staining and finding upstream vessels make VC detection easier and is recommended.

VC in small veins, deposition of collagen I and collagen IV, leading to white matter changes, was described in modified 2-vessel occlusion and hypertensive rats [22]. Venules can be differentiated from arterioles by α -smooth muscle actin staining. The study by Zhou et al. [23] used a renal artery occlusion model to induce hypertension in rats. Twenty weeks after surgery, there were increased visibility of the veins observed on the susceptibility-weighted imaging (SWI) and VC in the periventricular area on trichrome staining. However, LA was not observed. On the one hand, the observation period may have been not long enough for white matter damage to occur, which indicates that VC may have occurred before LA and, thus, could be an early marker of senile diseases. Compared with the former animal research, cerebral blood flow hypoperfusion may accelerate the pathological process of VC and LA. On the other hand, this model may be not associated with LA.

Neuroimaging Studies

Deep Medullary Veins

The potential for diagnosis and understanding of venous changes has been revolutionised by the development of MRI scans. SWI is widely used to demonstrate DMVs, as it can detect paramagnetic substances such as deoxyhaemoglobin in the blood and discriminate them from the parenchyma and the arteriole, appearing as hypo-intensities on images [24, 25]. DMVs, concentrating around the periventricular area, drain parenchyma around the periventricular area, including white matter. With regard to acute cerebral vascular diseases, DMVs on SWI scans exhibit the “brush sign” of veins, which occurs around the ischaemic area (as acute cerebral hypoperfusion increases the oxygen extraction in the veins), and this is widely accepted as a predictor of good outcomes [26, 27]. However, opinions are divided for chronic cerebral diseases.

In one study that tried to detect the veins from patients with carotid artery occlusion or stenosis, an increased number of patients with carotid artery occlusion showed a prominent signal and size of veins in the SWI phases [28]. Interestingly, in patients with carotid artery stenosis, who could benefit from collateral circulations, there were no significant changes in the veins. Hence, venous changes could be the consequence of arterial occlusion. Researchers have suggested that these results may be due to an increase in the oxygen extraction fraction, deoxyhaemoglobin, or the deoxyhaemoglobin/oxyhaemoglobin ratio. While they described the number, size, and signal density of DMVs, they did not specifically discuss the differences between them; the number and continuity changes of the DMVs may reflect different pathological mechanisms.

Yan et al. [4] observed an increased visibility of DMVs in LA patients. They measured the voxels of DMVs and LA volume. The results showed that the number of voxels was significantly higher in LA patients than in controls, and it was strongly associated with LA volume. They tried to explain the increase in number of voxels based on two points. First, cerebral blood flow hypoperfusion in the LA areas leads to increased oxygen extraction fraction in the venous system and promotes the visibility of DMVs. Second, the pathological changes in the veins, for example VC, leads to venous ischaemia and stenosis, which may induce dilation of the upstream venous bed (corresponding to the anatomy of DMVs) [29, 30].

However, studies on venous changes in CADASIL and multiple sclerosis (MS) patients showed some differenc-

es. A study in 13 CADASIL patients and 13 controls found that the number of DMVs was significantly lower in CADASIL patients [31]. Grey level values were used to count the number of DMVs; the reduction of DMVs was considered to be due to the loss of integrity in the microvasculature. Zivadinov et al. [32] also proposed that decreased visibility of DMVs in MS patients may result in chronic cerebrospinal venous insufficiency, which is an imbalanced state vascular condition involved with abnormal extracranial cerebrospinal venous routes. Another research on DMVs in MS patients counted DMVs by measuring the number of voxels, similar to the study by Yan et al. [4], and also found a significant loss of DMVs in MS patients compared to controls [33]. The decreased number of voxels of DMVs, which indicates decreased oxygen utilisation in MS patients, was in accordance with the results of a positron emission tomography study in MS patients that showed oxygen utilisation (including regional cerebral oxygen utilisation) and oxygen extraction were significantly reduced in the white matter hyperintensities of MS patients [34]. Interestingly, researchers suggest that “veins in lesions,” which were characterised as a hypo-intense dot or line in white matter lesions on fluid-attenuated inversion recovery, may be used to differentiate MS from CSVD [35].

From our observations, the stenosis or occlusion of DMVs leads to the disruption of venule compliance and the drainage system, resulting in the loss of integrity and continuity in SWI (Fig. 3). These controversial results of SWI studies may be due to the following reasons: first, the number of voxels is influenced not only by the concentration of deoxyhaemoglobin in the blood, but also by the size of the vessels, which in turn, is influenced by autoregulation of the cerebral blood flow [36]; second, the severity of VC, which induces luminal stenosis or even occlusion, changes with pathological progression. Since the voxel of DMVs cannot be used to discriminate the different stages of pathogenesis, the venous changes cannot be analysed just by number. Both morphological and metabolic changes should be considered when evaluating the DMVs. To resolve this problem, Zhang et al. [37] suggested a novel grading scale of DMVs on SWI, which is based on the visual assessment of continuous and homogeneous signals of DMVs, which may provide a method to further study the pathological changes of DMVs.

Retinal Veins

The pathological changes in retinal vessels are similar to those of vessels in the brain, as the anatomy, physiology, and embryology of both are similar [38, 39]. Chang-

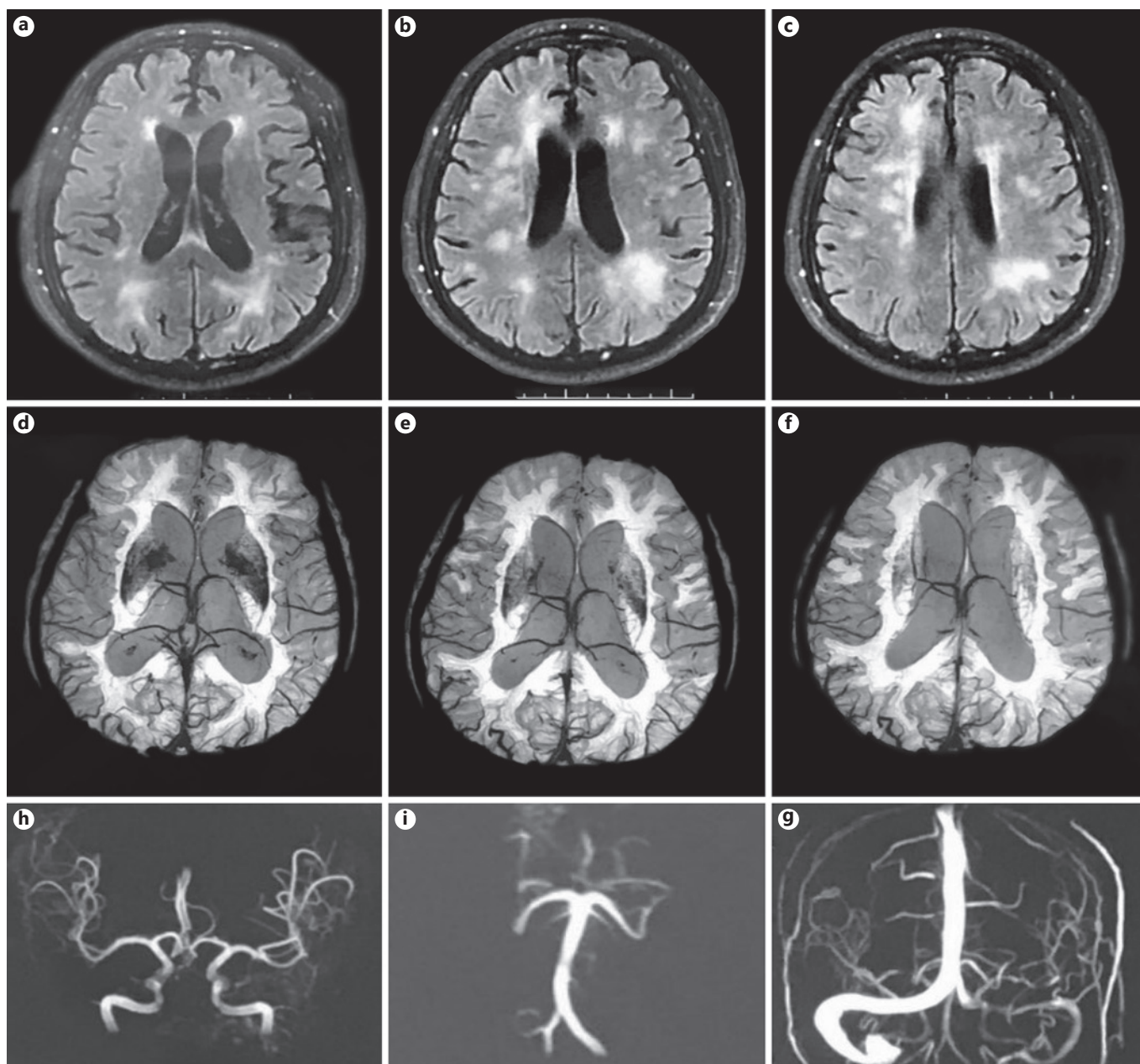


Fig. 3. A male 61-year-old patient developed severe cognitive impairment with leukoaraiosis due to venous collagenosis. **a–c** MRI showing leukoaraiosis around the ventricle, rated at grade 3 on the Fazekas grade scale. **d–f** Susceptibility-weighted images showing microbleeds around the periventricular area; integrated and con-

tinuous deep medullary veins are difficult to observe. **h, i** Magnetic resonance angiography images show that there are no stenoses or occlusion in large arteries. **g** Magnetic resonance venography image showing a thin transverse sinus on the right side, which is considered as a common congenital dysplasia.

es of retinopathy, including microaneurysms, retinal haemorrhage, and other less common lesions, were reported to increase the risk of developing LA 2.1- to 4.0-fold, similar to the pathological changes observed in atrophy studies [15, 16, 39]. In 2006, the Rotterdam scan

study reported that larger retinal venular diameters, but not smaller arteriolar diameters, were associated with progression of both periventricular and subcortical LA [40]. This dilation of venules may be attributed to retinal hypoxia [41]. In addition, taking into consideration the

post-mortem research by Moody et al. [15], another possible explanation could be that VC results in increased venous pressure, upstream venular dilation, and venular blood-brain barrier disruption. Since pathological specimens of cerebral veins are difficult to obtain, retinal venous changes could be used as an early marker of LA; ophthalmological examination in vivo offers a convenient way for evaluating pathological changes of the microvasculature. Lau et al. [42] developed an automated retinal image analysis software that could detect LA burden in 180 healthy adults, which could benefit the clinical evaluation of CSVD patients.

Internal Jugular Vein and Jugular Venous Reflux

Extracranial artery stenosis has been reported to be related to CSVD [43]. Regarding the extracranial venous system, Zivadinov et al. [32] systematically reviewed the extracranial venous system abnormalities and CNS diseases, in which extracranial venous abnormalities were separated into structural/morphological abnormalities, haemodynamic/functional abnormalities, and those determined only by the composite criteria and use of multimodal imaging. The pathophysiology of extracranial venous abnormalities, including decreased cerebral perfusion, cerebral microvascular damage due to increased cerebral venous hypertension, and altered cerebrospinal fluid dynamics, were associated with CNS disease and aging [44]. The internal jugular vein is the most important extracranial venous outflow pathway for the cerebral venous system to collect the venous flow [45]. Hence, blood flow changes in the internal jugular vein, especially jugular venous reflux (JVR), can induce blood flow autoregulation of the DMVs. There is research that noted JVR could double the LA score in patients older than 75 years [46]. In another study on AD patients, mild cognitive impairment patients and healthy controls, researchers demonstrated that subjects with severe JVR had more frequent hypertension, severe LA, and increased cerebrospinal fluid volumes [47]. Studies on idiopathic Parkinson's disease demonstrated that 57% of patients with idiopathic Parkinson's disease showed severe venous abnormalities, and the severity was associated with both LA and flow abnormalities [48].

JVR, which occurs with aging and could be induced by the Valsalva manoeuvre, elevates venous pressure by sustained or long-term repetitive retrograde-transmitted venous pressure and could lead to venous outflow insufficiency [30, 49]. This can result in the reduction of cerebral perfusion, reconstruction of the small vessel and disturbance of blood flow autoregulation, which could in turn

lead to VC and aggravate the pathological changes of LA. Though JVR was associated with LA in AD and Parkinson's disease patients, the sample sizes were small in these studies. Further studies with larger sample sizes are needed to investigate the mechanisms.

Conclusion

In this review, we analysed studies on disruption of the venous system in LA. Previous autopsy studies have demonstrated that LA is associated with arteriolar changes, the thickening of the venous wall (deposition of collagen), and luminal stenosis of the veins. In aging subjects, AD patients, and CADASIL patients, VC could be observed on trichrome staining, which begets the question: "Is VC the reason or the outcome of LA?"

The following are the possible mechanisms by which VC could induce LA. First, luminal stenosis or occlusion in the veins increases resistance of the vessel and venule pressure and decreases cerebral blood flow, leading to venous ischaemia. Second, venous occlusion in DMVs may influence the drainage system in the periventricular white matter; thus, occlusion of the vessel by interstitial fluid could lead to vasogenic oedema, resulting in the disruption of the blood-brain barrier.

It has been 20 years since VC was first reported in LA by Moody et al. [15]. Post-mortem and in vivo studies have been conducted to confirm the relationship between VC and LA. However, there is little animal research on VC, which may be due to a lack of animal models for VC research. In conclusion, disruption of the venous system is associated with LA in aging, AD, and CADASIL patients. The pathological changes in the venous system may induce cerebral hypoperfusion, drainage system disruption, and vasogenic oedema in the veins around the periventricular white matter. The clarification of VC in LA may provide an early prevention and early treatment for LA patients. Further research is required to identify specific mechanisms.

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Statement of Ethics

Written informed consent was obtained from the patients for the publication of this article. A copy of the written consent is available for review by the journal.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jiachun Feng and Di Ma conceptualized and designed the study; Di Nan and Yingying Cheng performed literature research and drafted the manuscript; Liangshu Feng and Mingming Zhao revised it critically and contributed to the writing of the manuscript. All authors have read and approved the final version of the paper.

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