REVIEW

An overview of cerebral venules: From structure, pathology, and imaging to related diseases

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Abstract: The cerebral microvascular system, which includes arterioles, capillaries, and venules, has often been studied as a whole in the past. Compared to the small arteries, we know very little about cerebral venules. Venous collagenosis was first proposed by Moody in 1995. With the development of imaging techniques, we can visualize cerebral venules *in vivo* by susceptibility-weighted imaging. There is a growing evidence that cerebral venules are associated with related neurological disorders such as cerebral small vessel disease, Alzheimer's disease, and multiple sclerosis. However, the risk factors leading to functional and structural alterations in the cerebral venules and the associated pathogenic mechanisms are not yet known. In this article, we review and summarize the studies related to cerebral venules.
Keywords: cerebral venules; anatomy; pathology; imaging; neurological disorders.

INTRODUCTION

Cerebral venules are often defined as veins <300 μm in diameter. Their main function is to drain blood from the cerebral cortex and parenchyma to the superficial pial veins or subependymal veins. After long-term overlook, recent evidence suggests that venules might play an important role in several neurological disorders. In 1995, the proposal of venous collagenosis (VC) (Moody *et al.*, 1995) brought attention to the pathological changes in cerebral venules. At the pathological level, VC was shown to be associated with leukoaraiosis and was considered to be one of the basic pathological changes in cerebral small vessel disease (CSVD) (Pantoni, 2010). The pathology of veins and venules is becoming increasingly important not only in CSVD but also in Alzheimer's Disease (AD) and multiple sclerosis (MS). Examples include venous amyloid deposition in patients with AD and perivenular inflammation and venulitis in patients with MS. At the imaging level, changes in the density, continuity, morphology, and number of cerebral venules can be observed. These imaging changes were also shown to be closely associated with neurological disorders such as CSVD, AD, and MS. For a better understanding of the function and potential role of cerebral venules, in this review, we summarize the following aspects of the cerebral venules – anatomy, microstructure, function, pathology, neuroimaging, and associated neurological disorders.

METHODS

We searched and scanned PubMed and EMBASE databases for articles related to cerebral venules published through February 2023.

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We used the following keyword combinations for the search: ("cerebral vein" OR "cerebral venule" OR "deep medullary vein" OR "cerebral venous system" OR "VC" OR "venous pathology") AND ("anatomy" OR "microstructure" OR "function" OR "glymphatic" OR "pathology" OR "neuroimaging" OR "CSVD" OR "AD" OR "amyloid beta-protein" OR "Aβ" OR "β-amyloid protein" OR "MS"). No language restriction was applied. After a review of titles, abstracts, text, and references for the articles, more were identified and screened. We selected clinical and animal experimental articles, autopsy pathology articles, and reviews that provide information on the anatomy, microstructure, function, pathology, imaging, and related diseases of the cerebral venules.

ANATOMY

The intracranial venous system is classified as the superficial cerebral venous system, deep cerebral venous system, and posterior fossa venous system (Khalatbari *et al.*, 2021). This review discusses on the small vessel anatomy of the superficial and deep cerebral venous systems. A schematic diagram of the coronal anatomy of cerebral venules is shown in Figure 1. The venules of the cerebral hemispheres consist of pial and parenchymal venules (Okudera *et al.*, 1999; Taoka *et al.*, 2017). The parenchymal venules can be divided into superficial parenchymal venules, deep parenchymal venules, and transcerebral and anastomotic medullary venules (Okudera *et al.*, 1999; Taoka *et al.*, 2017).

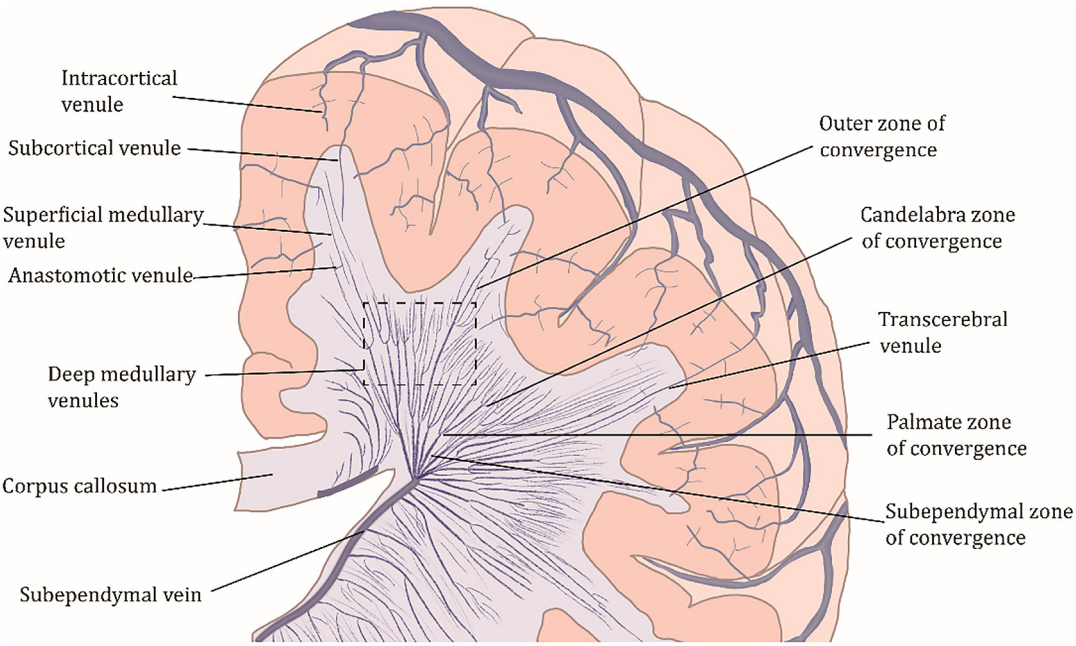

Figure 1. Schematic diagram of the anatomical structure of cerebral venules.

Superficial parenchymal venules are named according to their origin and include intracortical venules, subcortical venules, and superficial medullary venules (Khalatbari *et al.*, 2021; Okudera *et al.*, 1999; Taoka *et al.*, 2017). The intracortical venules are located within the cortex, the subcortical venules originate close to the white matter of the cortex, and the superficial medullary venules are located slightly deeper in the white matter. These venules drain the outer cortex and flow into the pial veins that are on the surface of the cortex (Friedman, 1997; Khalatbari *et al.*, 2021; Schmidek *et al.*, 1985).

The deep parenchymal veins drain the deep cerebrum, including deep medullary venules and subependymal veins (Khalatbari *et al.*, 2021; Okudera *et al.*, 1999; Taoka *et al.*, 2017). The deep medullary venules are long, fine vessels located in the lateral paraventricular white matter region, generally running perpendicular to the long axis of the lateral ventricles (Friedman, 1997; Hooshmand *et al.*, 1974). They run parallel to each other and form four zones of convergence in the frontoparietal region – outer, candelabra, palmate, and subependymal – and eventually converge to the subependymal veins (Hooshmand *et al.*, 1974; Khalatbari *et al.*, 2021; Okudera *et al.*, 1999; Schmidek *et al.*, 1985).

The superficial venous system and the deep venous system are connected by transcerebral and anastomotic medullary venules (Khalatbari *et al.*, 2021; Okudera *et al.*, 1999). Transcerebral veins directly penetrate the white matter of the brain, connecting the superficial cerebral (or pial) veins and subependymal veins in the ventricular wall. The anastomotic medullary venules are short venules bridging the superficial and deep medullary veins, which are difficult to visualize on conventional imaging due to their small diameter.

MICROSTRUCTURE

In previous studies and textbooks of human brain pathology, veins <300 μm in diameter were defined as venules, and arteries <200 μm in diameter were defined as arterioles. On the basis of luminal diameter and perivascular elements, venules can be roughly classified as postcapillary venules, collecting venules, muscular venules, and small collecting veins (Rhodin, 1968; Takahashi *et al.*, 1994).

Human blood vessel walls are physiologically composed of three layers, including intima, media, and adventitia (Figure 2). Arterioles usually have a complete three-layer structure. The endothelium forms a complete continuous layer with a thick basement membrane; the media has 1–3 layers of smooth muscle cells; the outer layer is relatively thin (Dahl, 1973; Roggendorf *et al.*, 1977). Venules are structurally different from arterioles, they do not have a vessel wall consisting clearly of endothelium, media, and adventitia (Roggendorf *et al.*, 1978; Schmidek *et al.*, 1985). Venules typically have thinner walls and larger lumen than arterioles. In addition, cerebral veins lack valves and blood flow is possible in different directions (Uddin *et al.*, 2006). Compared to arterioles with a regular smooth muscle cell layer, the smooth muscle layer of the venous intima is thinner and usually has only a lightly stained layer of vascular smooth muscle cells (Cao *et al.*, 2021). The structural feature of lack of support from the smooth muscle cell layer makes the veins more prone to collapse. Because of the lack of collateral drainage, occlusion of multiple small cerebral veins may be more severe than occlusion of large veins and dural sinuses (Moody *et al.*, 1995).

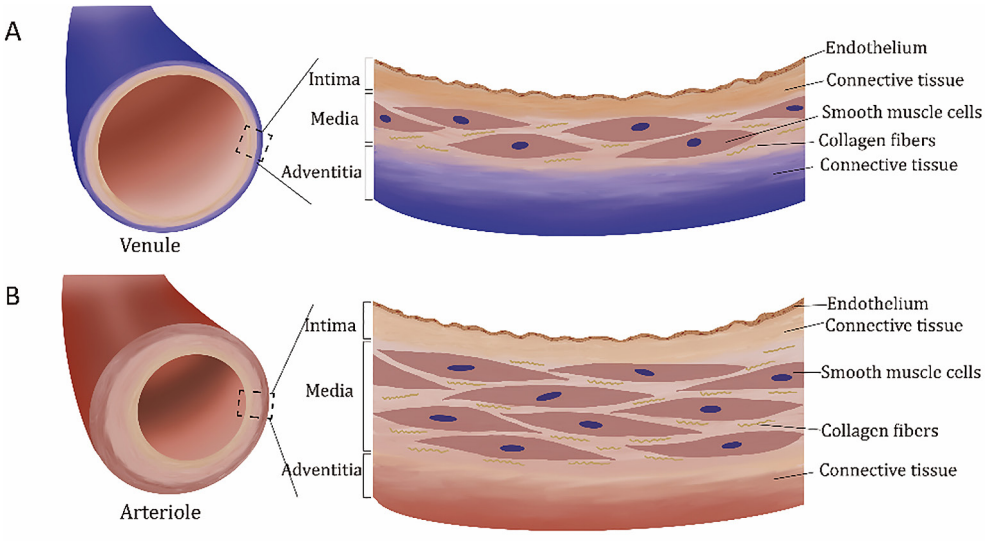

Figure 2. Comparison of the vessel wall structure of venules and arterioles. (A) Diagram of the wall structure of the venule. (B) Diagram of the wall structure of arteriole.

FUNCTION

The primary function of the cerebral veins is to perform blood transport and remove carbon dioxide and other metabolic wastes from the cerebral vascular network. Cerebrospinal fluid (CSF) was thought to be reabsorbed through the subarachnoid granules into the venous sinuses for outflow, although the extent to which arachnoid granulations are implicated in CSF drainage was questioned (Ringstad *et al.*, 2017). The cerebral venous system plays an important role in maintaining the homeostasis of cerebral perfusion and in the regulation of intracranial pressure. Venules are important contributors

to cerebrovascular resistance, but their role in regulating blood flow is minimal under physiological conditions (Kulik *et al.*, 2008). Venous endothelium is involved in forming the blood-brain barrier (BBB). Postcapillary venules may be involved in the migration of cells from the blood to the cerebral parenchyma (Owens *et al.*, 2008).

In recent years, the glymphatic system was proposed as a brain-wide pathway for the clearance of metabolic waste (Iliff *et al.*, 2012; Jessen *et al.*, 2015). CSF enters the brain via periarterial spaces and exchanges with the surrounding interstitial fluid (ISF), then ISF and interstitial solutes were drained along the perivenous spaces. The interstitial bulk flow between these influx and efflux pathways depends on perivascular astrocytic aquaporin-4(AQP4) (Iliff *et al.*, 2012). The most important function of the glymphatic system may be the removal of metabolic waste through perivenous spaces. A previous study found that deletion of AQP4 channels reduced exogenous amyloid β (Aβ) clearance by 65%, which may indicate that the glymphatic system is an important contributor to Aβ clearance in the brain (Iliff *et al.*, 2012). The function of cerebral venules has not been adequately studied. The proposal of the glymphatic system indicates an important role of the cerebral venous system, which deserves further research and exploration.

PATHOLOGY

Development of pathological staining techniques

Several staining methods have been proposed in previous human histopathology studies to distinguish venules from arterioles. As early as 1995, (Moody *et al.*, 1995) used alkaline phosphatase as a protein marker to differentiate between venules and arterioles. The application of this method is limited by the stringent requirements for alkaline phosphatase activity. Thus, it was hardly used in subsequent pathological studies on venules. Subsequently, (Shen *et al.*, 2012) used a new fluorescent dye (Alexa Fluor 633) to specifically label elastin in arteries and arterioles. Some other studies (Keith *et al.*, 2017; Lahna *et al.*, 2022) stained the smooth muscle cells in the arterial vessel wall by anti-α-smooth muscle actin immunohistochemical staining. However, it is important to note that smooth muscle cells and elastin can degenerate in the pathological state and may not be left for staining. Recently, Cao *et al.* found that monocarboxylate transporter 1 (MCT1) specifically expressed in venous endothelial cells could be stained to distinguish between venules and arterioles (Cao *et al.*, 2021; Vanlandewijck *et al.*, 2018). They found that the anti-MCT1 immunostaining method can accurately differentiate venules and arterioles, especially when collagen deposits are present in the vessel wall.

Despite the urgent need, there are still only a few neuropathological studies of small veins till date. This may be because reliable pathological staining methods for identifying venules and arterioles are still being explored. With the continued development of these staining techniques, we can better distinguish venules from arterioles at the pathological level. A clear method of identifying venules is also important for future studies on the pathology and pathogenesis of venules.

VC

VC was first proposed in 1995 by (Moody *et al.*, 1995). They identified a previously unrecognized, non-inflammatory, mural disease of the periventricular veins. The characteristic pathological changes of these periventricular veins are luminal narrowing combined with concentric collagen thickening of the vessel wall. Although VC has been recognized as a subgroup of CSVD (Pantoni, 2010), there is still a paucity of studies on the pathology of cerebral venules.

The available pathological findings suggested a potential correlation between VC and the severity of leukoaraiosis (Keith *et al.*, 2017; Lahna *et al.*, 2022; Moody *et al.*, 1995; Pettersen *et al.*, 2017). (Moody *et al.*, 1995) stained brain tissue from 22 autopsy patients and found that advanced leukoaraiosis was present in the majority of patients with VC. Leukoaraiosis appears as white matter hyperintensities (WMH) on T2 MRI. In an autopsy study, (Keith *et al.*, 2017) investigated the relationship between periventricular VC or cerebral vein stenosis and white matter lesions. He classified veins into small, medium, and large caliber veins. The results showed that VC in small and medium veins and stenosis ratio in large veins were both positively correlated with WMH. The potential association of VC with WMH was also reported in a postmortem study of a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Pettersen *et al.*, 2017). This patient was found to have pathological changes of VC in the WMH. In a recent study, (Lahna

et al., 2022) analyzed the association between VC and WMH in 25 subjects (mostly with AD). They reported that increased venous collagen but not arterial collagen was a significant predictor of higher periventricular WMH burden.

Some research evidence suggests that VC is a venous pathological change that accompanies aging (W. R. Brown *et al.*, 2002; Moody *et al.*, 1997). Moody *et al.* reported VC of the periventricular veins in 65% of patients aged ≥60 years (Moody *et al.*, 1995). In a recent venous pathology study (Cao *et al.*, 2022), it was noted that VC is widespread in the aging brain and also shows a significant positive correlation with advancing age in most brain regions. This study found that VC can occur in different brain regions, such as the white matter region, cortical gray matter, and basal ganglia, most commonly in the periventricular occipital white matter region. There are also several studies suggesting an association between VC and AD. Keith *et al.* found VC combined with venous stenosis in the periventricular veins of AD patients (Keith *et al.*, 2017). Our team also compared cerebral microvascular pathological changes in patients with intermediate- or high- AD neuropathological changes (ADNC) and non-ADNC patients and found a higher proportion of VC in ADNC patients (unpublished data). The current studies show a correlation between VC and age, and whether VC is associated with the development of specific diseases deserves further study.

In human autopsy studies, the collagen components abnormally deposited in the walls of cerebral venules are mainly collagen I and III (W. R. Brown *et al.*, 2002, 2011). In the normal vessel wall, collagen I and III are widely distributed in the interstitial matrix. They are mainly produced by fibroblasts and usually appear together to form reticular fibers (Karsdal *et al.*, 2017; Kisling *et al.*, 2019). Collagen I is composed of strong, rigid fibers that primarily provide stiff mechanical support for the vessel walls (Tang, 2020). Collagen III fibrils are regarded as immature, weak, and elastic and are associated with dilation and elasticity of the vessel wall (S. R. Brown *et al.*, 2017). Increasing the collagen I/III ratio provides tissue structural rigidity while decreasing this ratio provides tissue elasticity and flexibility (Kisling *et al.*, 2019). The type of collagen thickened in the vessel wall and the ratio of collagen I/III may be related to morphological changes in aging vessels, such as tortuosity and dilatation. In an animal study, researchers used modified two-vessel occlusion (modified 2VO) (1-week interval bilateral carotid artery occlusion) in stroke-prone renovascular hypertensive rats (RHRSP) to establish a modified white matter lesion rat model (RHRSP/modified 2VO) to mimic the pathological changes of white matter lesions (Lin *et al.*, 2017). It was found that RHRSP/modified 2VO rats showed more severe collagen deposition in venules than RHRSP rats, and most of the deposition was of collagen I and IV, rather than collagen III. Collagen IV is the most abundant structural BM component and is essential for BM stability, but is not necessary for initial BM formation (Gatseva *et al.*, 2019; Poschl *et al.*, 2004). Type IV collagen is encoded by the COL4A1-COL4A6 genes, of which the COL4A1/2 genes are shown to be associated with hereditary CSVD (Whittaker *et al.*, 2022). It is important to explore what types of collagen deposits are present in the venous vascular wall for our understanding of VC. Considering the species differences between existing studies, further studies are needed in the future.

It is unclear what causes the appearance of VC and what are the associated pathogenic mechanisms. Some previous studies suggest that age (Moody *et al.*, 1995), hypertension (Lin *et al.*, 2017; M. Zhou *et al.*, 2015), and low perfusion (Pettersen *et al.*, 2017) may promote collagen deposition in the vessel walls. There is no direct evidence that the occurrence of VC is associated with specific genetic mutations. Brown *et al.* proposed the hypothesis that some individuals may have a genetic predisposition to develop VC (W. R. Brown *et al.*, 2009), but this hypothesis has not been confirmed in the available studies. VC is accompanied by luminal narrowing, the possible physiological consequences of which include decreased cerebral perfusion pressure, disruption of the BBB, and disturbance of venous drainage (Moody *et al.*, 1995). However, these potential risk factors and related pathogenic mechanisms have not been further confirmed in studies at present. In the future, we need more relevant studies to help us understand the causes and consequences of VC.

VENOUS AMYLOID

The deposition of amyloid in the walls of cerebral blood vessels is known as cerebral amyloid angiopathy (CAA) (Revesz *et al.*, 2003). There is a strong association between CAA and AD. Current studies attribute CAA and AD mainly to arterial and arteriolar pathology, with a minimal role for veins (Weller *et al.*, 2009; Weller *et al.*, 1998). Some evidence from preclinical (Cohen *et al.*, 2013; Joo

et al., 2017; Klakotskaia *et al.*, 2018) and clinical (Mendel *et al.*, 2013; Thal *et al.*, 2002; Weller *et al.*, 2009; Weller *et al.*, 1998) studies suggests the presence of amyloid deposits in the veins and venules.

Preclinical studies show venous amyloid deposition in multiple animal models of AD (Cohen *et al.*, 2013; Joo *et al.*, 2017; Klakotskaia *et al.*, 2018). Extensive Aβ deposition in the walls of cortical and leptomeningeal arteries and veins, as well as VC, was found in the APP+PS1 rat model (Klakotskaia *et al.*, 2018). Aβ accumulated in all layers of the leptomeningeal vein wall. In contrast, leptomeningeal arterial Aβ accumulated mainly in the adventitia and occasionally in the media layer. In a study of early neurovascular dysfunction in a rat model of AD, (Joo *et al.*, 2017) proved that vascular Aβ deposition was not confined to arterioles and that milder amyloid deposits can be found in venules of 9-month-old TgF344-AD rats. Evidence from clinical studies also supports the presence of Aβ deposition in the veins of the brains of AD patients, although to a lesser extent than arterial Aβ deposition (Weller *et al.*, 2009; Weller *et al.*, 1998). (Weller *et al.*, 1998) performed thioflavin S staining on paraffin sections of leptomeninges from AD patients to quantify amyloid deposition in arteries and veins. They found that Aβ accumulated five times more frequently around arteries than around veins and that about 4.4% of veins were positive for amyloid. In a neuropathological study of 69 human autopsy brains, (Thal *et al.*, 2002) found that in patients with two types of CAA (presence or absence of Aβ in capillaries), both leptomeningeal and cortical veins showed Aβ deposition, suggesting that CAA is not exclusive to arteries.

The contribution of venous amyloid to the pathogenesis of CAA and AD is understudied. Nevertheless, the involvement of venous pathology in white matter lesions and other cerebrovascular diseases suggests that venules play an important role in contributing to dementia (Black *et al.*, 2009; Hartmann *et al.*, 2018). Even though venous Aβ deposition is rare, it may be an integral part of AD pathogenesis, leading to cerebrovascular dysfunction and impaired Aβ clearance mechanisms (Greenberg *et al.*, 2020; Morrone *et al.*, 2020).

PERIVENULAR INFLAMMATION AND VENULITIS IN MS

The involvement of the cerebral venous system in MS has been recognized for many years. The anatomical distribution of MS plaques exhibited a periventricular, perivenular distribution. On pathology, irregular venous stenosis and dilatation with associated venous wall and perivenous infiltration can be observed.

As early as the nineteenth century, pathological studies reported the central vessels in MS plaques (Rae-Grant *et al.*, 2014). In 1915, pathologist James Walker Dawson described the MS lesions as plaques concentrated around the ventricles and distributed along the veins, which appear finger-like and are now commonly referred to as "Dawson's fingers". The presence of perivascular cuffs can be observed in histopathology. Inflammatory cells, fibrinoid exudate within and around the vessel wall, and perivascular iron deposition make up the perivascular cuff (Adams, 1988; Tanaka *et al.*, 1975).

A pathological study of MS patients showed the presence of fibrinous exudates and other humoral inflammatory factors in and around venules in both active lesions and normal white matter (Adams *et al.*, 1985). The veins and venules within or distant from active lesions usually showed an inflammatory lymphocytic reaction and may be confined to the vessel wall (Adams *et al.*, 1985). When confined to the vein wall, these inflammatory changes may be considered a form of localized venous vasculitis or cerebral venulitis (Adams *et al.*, 1985). As the disease progresses, the cellular infiltrate appears to spread to the perivascular space and even into the adjacent tissue. Intimal hyperplasia and collagenous thickening of venular walls are noted and are thought to be a consequence of chronic inflammation. Further studies by (Adams, 1988) showed that the cerebral vein wall in MS is affected by chronic inflammatory damage, contributing to hemorrhage and increased permeability, and constituting a form of vasculitis. Although these processes are non-specific, they do indicate the presence of an inflammatory process in the MS vein wall, resulting in damage and thickening. These findings suggest that venous wall damage is an important aspect of MS plaque pathology. (Kapadia *et al.*, 2020) proposed the hypothesis that MS is a primary autoimmune vasculopathy.

NEUROIMAGING STUDIES OF CEREBRAL VENULES IN NEUROLOGICAL DISORDERS

Development of imaging techniques

In recent years, imaging studies of cerebral venules have evolved considerably with improved imaging techniques. The structure and function of small veins can be examined *in vivo* with ultrahigh-field

MRI. In the past, it was difficult to visualize cerebral venules with conventional imaging techniques, but the emergence of a new imaging technique, susceptibility-weighted imaging (SWI), has opened a new era in the study of cerebral venules. SWI can show the cerebral venous vascular network *in vivo* by using paramagnetic deoxyhemoglobin in venous blood as an endogenous contrast agent (Haacke *et al.*, 2004; Reichenbach *et al.*, 1997). Small cerebral veins with diameters of 100–500 μm can be visualized using 3T SWI combined with phase-map enhanced contrast and minimal density projection techniques. In addition, 3T MRI enables quantitative analysis of venous blood voxels by segmenting brain venous structures on SWI phase data, which is worthy of further use in future studies (Ge *et al.*, 2009; Yan *et al.*, 2014). The deep medullary veins (DMV) located in the lateral paraventricular are one of the most frequently evaluated small cerebral veins due to their low anatomical variability and relatively constant diameter. On imaging, DMV may show changes in venous density, continuity, symmetry, morphology, and volume. These imaging changes of cerebral venules may suggest the presence of associated neurological disease. Analysis of cerebral venules by SWI technique has some limitations, as the intensity of venous visualization is influenced by the deoxyhemoglobin content. Increased visualization of cerebral venules may occur when there is hypoperfusion, hypoxia, or anemia due to large artery stenosis. Subsequent developments in 7T MRI have enabled full visualization and quantification of DMV (Bernier *et al.*, 2018; Kuijf *et al.*, 2016). 7T MRI provides multidimensional information on the number, diameter, length, total volume, and tortuosity of DMV using automated extraction and 3D reconstruction of vein morphology, with excellent reproducibility and a good positive predictive value (Kuijf *et al.*, 2016). However, the current high cost of acquiring imaging data from 7T MRI limits its use in clinical studies with large samples. Functionally, phase contrast MRI imaging and 4D flow MRI techniques allow for the assessment of intracranial venous blood flow and pulsatility (Blair *et al.*, 2020; Rivera-Rivera *et al.*, 2017; Y. Shi *et al.*, 2020).

CSVD

CSVD is a pathological process affecting the small vessels of the brain, including small arteries, arterioles, small veins, and capillaries, with a variety of etiologies (Pantoni, 2010). Features observed on neuroimaging include WMH, lacunes, enlarged perivascular spaces, recent small subcortical infarcts, microbleeds, and brain atrophy (Ter Telgte *et al.*, 2018). In recent years, the role of small cerebral veins in CSVD received increasing attention as they can be visualized in images. Much of the current literature suggests that imaging changes in DMV correlate with the radiological markers of CSVD.

The association of DMV with WMH is the most frequently reported. Several cross-sectional studies analyzed the correlation between DMV and WMH, but the results obtained were inconsistent. One study reported that the density of small veins both within and outside WMH was significantly lower in CADASIL patients than in controls (De Guio *et al.*, 2014), suggesting that the decrease in density of small veins appeared earlier than the white matter lesion. (R. Zhang *et al.*, 2021; R. Zhang *et al.*, 2017) found that decreased number and continuity of DMV are associated with an increased volume of WMH and may cause white matter damage. In contrast, (Yan *et al.*, 2014) reported that the increased number of voxels in DMV was positively correlated with WMH volume. The reasons for the inconsistent findings may be that the pathological changes in the cerebral venules may be a dynamic process, as well as the increased compensatory oxygen uptake due to reduced cerebral perfusion (Yan *et al.*, 2014). In another community cohort population study, the number of DMV was found to be independent of WMH volume (Ao *et al.*, 2021) and negatively associated with cerebral white matter microstructural damage (Liu *et al.*, 2022). There was some variation in the findings across studies due to inconsistent testing methods and the inclusion of populations, which may require further validation in a longitudinal cohort.

There are also several studies conducted in patients with CSVD showing an association between disruption of the DMV and lacunes (Chen *et al.*, 2020; Xu *et al.*, 2020; Y. Zhou *et al.*, 2020), enlarged perivascular spaces (Xu *et al.*, 2020; K. Zhang *et al.*, 2022), microbleeds (R. Zhang *et al.*, 2019), and brain atrophy (Chen *et al.*, 2020). The CSVD score integrates multiple imaging markers into a unitary measure and therefore provides a more comprehensive picture of the overall changes and severity of brain tissue (Amin Al Olama *et al.*, 2020; Staals *et al.*, 2015). Two cross-sectional studies scored CSVD burden and found a strong positive correlation between reduced DMV visibility in SWI and the severity of CSVD (Chen *et al.*, 2020; Xu *et al.*, 2020).

The altered DMV on imaging may reflect periventricular VC at the pathological level (Xu *et al.*, 2020). However, we need to be aware that the same CSVD markers observed on imaging may be heterogeneous in terms of pathological presentation (Ter Telgte *et al.*, 2018). In addition, lesions may be present at the pathological level long before they are observed on imaging. The combined use of imaging and pathological techniques in future studies may help to further explore the pathogenesis of cerebral venules.

AD

Morphological changes in the DMV were also observed on imaging in patients with AD. A 7T MRI study based on a community elderly population found that periventricular venules were significantly tortuous in the elderly and that a greater venous tortuosity ratio was associated with APOE4 (Shaaban *et al.*, 2017). Another cross-sectional study (Bouvy *et al.*, 2017) compared DMV between patients with early Alzheimer's disease (eAD) or amnestic mild cognitive impairment (aMCI) and controls. It was found that the number and density of DMV in eAD and aMCI were similar to controls, but venous tortuosity was significantly increased. Two community-based population studies (Ao *et al.*, 2021; Liu *et al.*, 2022) showed that a reduced number of DMV was associated with brain atrophy. In a community cohort population of 1056 participants, (Ao *et al.*, 2021) used the 3T SWI method to assess the correlation between the number of DMV and brain structure. Their study showed that the reduction in DMV numbers was not only associated with lower whole brain volume but also with lower gray matter, white matter, and hippocampal volume. Further studies based on this community population showed that DMV-associated atrophy was predominantly distributed in the bilateral occipital lobe, middle and inferior temporal lobe, and hippocampus (Liu *et al.*, 2022), overlapping with the distribution of AD-associated atrophy (Bakkour *et al.*, 2013), suggesting that cerebral venules may be involved in the pathological process of neurological degeneration. Several studies reported that the retinal veins, which are embryologically homologous to the small cerebral veins, were more likely to develop venous stenosis and tortuosity in AD patients (Cheung *et al.*, 2014; H. Shi *et al.*, 2021).

MS

MS is an immune-mediated inflammatory demyelinating disease of the central nervous system with multifactorial pathogenesis (Compston *et al.*, 2008). With the development of SWI techniques, we can observe the central veins in MS plaques *in vivo* (Reichenbach *et al.*, 1997; Tan *et al.*, 2000). The perivenous distribution of MS plaques was further confirmed in subsequent studies using high-resolution 7T MRI (Hammond *et al.*, 2008; Tallantyre *et al.*, 2008). In addition, MS plaques distributed along perivenous were found in all clinical phenotypes of MS (relapsing-remitting MS, secondary progressive MS, and primary progressive MS) (Kilsdonk, Lopez-Soriano, *et al.*, 2014; Kuchling *et al.*, 2014). The central vein sign (CVS) is considered to be one of the imaging features of MS (Sati *et al.*, 2016). In a prospective longitudinal cohort study, Mistry *et al.* found that the central vein detected in white matter lesions is a specific diagnostic biomarker for inflammatory demyelination and may also contribute to the diagnosis of MS (Mistry *et al.*, 2013). Several studies showed that CVS can distinguish MS from its mimics (Kister *et al.*, 2013; Sinnecker *et al.*, 2012), including distinguishing MS lesions from vascular white matter lesions (Kilsdonk, Wattjes, *et al.*, 2014; Mistry *et al.*, 2016).

Evidence from several cross-sectional-based studies found that periventricular DMV is associated with MS. A 3T SWI imaging study showed a significant decrease in the visibility of the periventricular white matter veins in patients with relapsing-remitting MS compared to controls (Ge *et al.*, 2009). Another study used 7T MRI imaging and observed decreased density and visibility of the periventricular DMV in patients with MS (Sinnecker *et al.*, 2013). (Zeng *et al.*, 2013) concluded that reduced density and shortening of the DMV are seen in patients with long-course MS, while for patients with short-course MS, DMV is increased or elongated.

The etiology of MS is currently more often considered to be autoimmune. However, there is a long history of perivascular inflammation and growing evidence of a pathogenic role of vascular factors. Venous pathological changes in MS may involve multiple pathophysiological mechanisms, including endothelial dysfunction, VC, fibrin deposition, loss of vessel compliance, venous hypertension, and decreased cerebral perfusion (Haacke *et al.*, 2021).

CONCLUSION

The venous system plays a complex role in maintaining the homeostasis of cerebral perfusion, the composition of the BBB, and other physiological functions. As a relatively new field of research, the pathophysiological mechanisms of cerebral venules in various neurological diseases need to be further investigated. With the development of pathological and imaging techniques, cerebral venules are expected to be a new direction to explore the cerebral microvascular system. An in-depth exploration of cerebral venules will help us to fully understand related diseases, elucidate the mechanisms, and explore therapeutic targets.

Conflict of Interest Disclosure

The authors declare that they have no conflict of interest.

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Abbreviations

VC	Venous collagenosis
CSVD	Cerebral small vessel disease
AD	Alzheimer's Disease
MS	Multiple sclerosis
CSF	Cerebrospinal fluid
ISF	Interstitial fluid
AQP4	Aquaporin-4
MCT1	Monocarboxylate transporter 1
WMH	White matter hyperintensities
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
ADNC	Alzheimer's Disease neuropathological changes
RHRSP	Stroke-prone renovascular hypertensive rats
BBB	Blood-brain barrier
CAA	Cerebral amyloid angiopathy
Aβ	Amyloid β
SWI	Susceptibility-weighted imaging
DMV	Deep medullary veins
eAD	early Alzheimer's disease
aMCI	amnestic mild cognitive impairment
CVS	Central vein sign

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