# Cerebral Small Vessel Disease

Subjects: Others

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Cerebral small vessel disease (CSVD) represents a cluster of various vascular disorders with different pathological backgrounds. The advanced vasculature net of cerebral vessels, including small arteries, capillaries, arterioles and venules, is usually affected. Processes of oxidation underlie the pathology of CSVD, promoting the degenerative status of the epithelial layer. There are several classifications of cerebral small vessel diseases; some of them include diseases such as Binswanger's disease, leukoaraiosis, cerebral microbleeds (CMBs) and lacunar strokes.

Keywords: CSVD ; CMB ; cerebral microbleeds ; cerebral small vessel disease

## 1. Introduction

Cerebral small vessel disease (CSVD) represents a cluster of pathologies with a heterogeneous etiology and a pathomechanism affecting elements of the brain vascular system such as small arteries, capillaries, arterioles and venules. Histopathologic studies demonstrate reduced lumens in affected vessels and also demonstrate the thickening of walls, which impedes perfusion and transmural gas transfer [1]. The disease accounts for 20–30% of cases of ischemic stroke [2][3] and cerebral hemorrhage [4][5]. Moreover, CSVD has been shown to worsen functional outcomes after supra [6] and infratentorial [7] ischemic stroke because it disrupts the reorganization of brain networks that is essential for post-stroke recovery. Certain fluid biomarkers have been identified to correlate with CSVD. Some studies present elevated levels of Low Molecular Weight Neurofilament Protein (NF-L), tissue inhibitor of metalloproteinase-1, metalloproteinase-9 and metalloproteinase-2 in CSVD patients [8]. Imaging examination has revealed a direct relationship between Alzheimer's Disease occurrence and certain identified cerebral vascular diseases, principally CSVD.

CSVD can be classified according to varied pathological, radiologic and clinical criteria. Most commonly, two types are identified: amyloid and non-amyloid related. CSVD has been recognized as a dynamic condition of the whole brain and as having a diffuse nature, and systems for the visual scoring of MRI images have been introduced to assess the total load of the disease [9][10]. The neuroimaging features are white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), lacunae, subcortical infarcts, microbleeds and brain atrophy. Some researchers include individual disease entities in this group, such as Binswanger's disease, leukoaraiosis, cerebral microbleeds (CMBs) and lacunar strokes.

## 2. Classification of Cerebral Small Vessel Disease

CSVD can be divided into six groups:

- Type I: arteriosclerosis/age-related CSVD;
- Type II: amyloid-related CSVD;
- Type III: genetic CSVD distinct from amyloid angiopathy;
- Type IV: inflammatory/immunologically mediated CSVD;
- Type V: venous collagenosis;
- Type VI: other CSVD.

## 3. Etiology of Cerebral Small Vessel Disease

The deposition of amyloid-beta in the cerebral vessels (cerebral amyloid angiopathy (CAA)) is a common finding in elderly people, a major cause of spontaneous intracerebral hemorrhage (ICH) and an important contributor to age-related mental decline [11]. The accumulation of eosinophilic hyaline material along the basement membranes is accompanied by progressive loss of the smooth muscle layer in the media of arterioles [12]. This results in the formation of microaneurysms

and a temporary blockage of the vessel lumen [13]. However, the exact etiology of these lesions remains unknown. Some authors associate amyloid deposition in CAA with its production in smooth muscle cells after earlier damage [14][15]. The neuronal origin of β amyloid, which in the next stage would be transported into the blood along the fluid spaces around the cortical and meningeal arteries, has also been suggested [16][17]. Other theories concern the damage to the blood–brain barrier, which determines the penetration of its molecules [18][19].

The pathological hallmarks of CAA, first described in 1954 by Stefanos Pantelakis, have since been confirmed by more recent studies: the involvement of arterioles of the meninges and cerebral cortex, favoring posterior regions of the brain (occipital lobes), the sparing of white matter vasculature, association with age and dementia, a lack of association with hypertension and atherosclerosis (unlike other CSVD) and independence from systemic amyloidosis [20]. Cerebral microvessels are crucial for the drainage of interstitial fluid of the brain; thus, the accumulation of amyloid-beta is an early sign of clearance failure and has pending hemorrhagic or ischemic consequences [21]. In an autopsy, the condition can be detected in 20–40% of the non-demented and 50–60% of the demented elderly population [22].

Although highly prevalent in patients affected with Alzheimer's disease (found post-mortem in 85–95% of patients), it is rarely diagnosed during the patient's lifetime [23]. In MRI, biomarkers of CAA are lobar ICH, lobar microbleeds, cortical superficial siderosis, white matter hyperintensities (periventricular, posterior–predominant), enlarged perivascular spaces in the cerebral white matter and cortical microinfarcts. CAA lesions primarily affect the cortical vessels and those that supply the meninges. This determines the location of the markers detected in imaging tests. It has been shown that, in the case of changes caused by amyloid etiology, microbleeds, which are a sign of CSVD, are usually found in the cerebral and cerebellar lobes, including their cortical and subcortical areas [8]. Localization in the occipital lobe is particularly frequent [2]. It is also worth mentioning that the presence of such changes may also be genetically determined. An analysis of the genotype of apolipoprotein E showed its ε4 isoform to be associated with a greater prevalence of microbleeds. At the same time, it results in a greater ratio of β-amyloid 40 to β-amyloid 42 [24]. CAA has been classified into two pathological types: CAA type 1, characterized by amyloid in cortical capillaries; and CAA type 2, where amyloid deposits are found in leptomeningeal and cortical arteries, but not capillaries [15].

Another key factor in the etiology of cerebral small vessel disease is hypertensive angiopathy—the umbrella term for a spectrum of sporadic non-amyloid small vessel pathologies associated with age, hypertension, diabetes mellitus and other vascular risk factors. Pathologically, it is characterized by the narrowing of the vessel lumen resulting from the collagenous hypertrophy of the vascular wall and exudation of serum proteins [1]. This type of microangiopathy predominantly affects the small perforating arteries of the deep grey nuclei and deep white matter [25]. As a consequence, the bleedings caused by this condition occurs in deep-brain regions (e.g., the basal ganglia, thalamus and brain stem). Distinguishing CAA from hypertensive angiopathy may have clinical implications (which is relevant for treatment decisions concerning antithrombotic use), as CAA-related lobar ICH carries a considerably higher risk of recurrence [26].

Recent studies have proven that oxidative stress is also a major factor influencing different types of CSVD. Oxidative stress is caused by disturbances of the homeostasis between oxidation and antioxidation processes. An imbalance occurs when free radicals increase or antioxidation processes become inefficient [27][28]. Molecular oxygen undoubtedly plays key roles in the biology of every cell, thus affecting tissues and systems and consequently the entire organism; it is necessary for proper functioning and life [29][30][31]. Although oxygen is important as a life-determinant and is also involved in signal transduction, the regulation of gene transcription and the control of other cellular activities, it also has a detrimental effect on biomolecules in the form of reactive oxygen species (ROS) and free radicals. The unfavorable effect of oxygen is due to its monovalent reductive status, which is directly responsible for ROS production [29][30][32]. Oxygen is an irreplaceable entity for all living organisms, although its presence in excess has harmful effects. Therefore, it is required that the consumption and uptake of oxygen be maintained under a high level of control and that the levels are checked by a complex cell system [32][33][34][35]. Uncontrolled redox reactions generate ROS, such as hydroxyl radicals (•OH), superoxide anions ($•O_2^-$), peroxyl radicals (ROO•), hydrogen peroxide ($H_2O_2$) and nitric oxide (NO•). Hydrogen peroxide ($H_2O_2$) and superoxide anion ($O_2^-$) constrict vessels, reducing blood flow [36][37][38][39]. Oxygen radicals activate inflammatory processes and the formation of oxidized low-density lipoprotein (LDL), affecting the vascular endothelial part of the vessel walls [40][41][42]. Oxidative stress is an indisputable factor contributing to vascular damage and loss of function. Nitric oxide is another important mediator that could be a target of the destructive influence ROS and carries out a regulatory function on vascular smooth muscle cells. It controls many processes such as proliferation and relaxation, vascular tone intensity, hemodynamics and angiogenesis [43][44]. Oxidative stress and ROS are commonly known as crucial factors in the etiology of CSVD. The endothelium, as a significant structure of the vessel architecture, regulates wall tone and maintains adequate perfusion. Many studies have revealed that the endothelium is the main target of inadequate oxidation, accelerating the degenerative effects on CNS blood flow in CSVD patients. Monovalent reactive

forms of free radicals are promoted by arterial hypertension, the oxidation of low-density lipoproteins (oxLDL), diabetes mellitus, a high level of homocysteine, general infections and cigarette smoking. Consequently, excessive ROS formation underlies the pathology of cerebral small vessel disease [45].

## 4. Detection of Cerebral Small Vessel Disease

The diagnosis of cerebral small vessel disease is based on the detection of neuroimaging markers occurring in the course of its development. They include a number of characteristic lesions that can be observed in imaging tests. This group includes cerebral atrophy, leukoaraiosis, white matter hyperintensities and cerebral microbleeds.

### 4.1. Cerebral Atrophy

Cerebral atrophy is a kind of condition in which neurons and the connections between them are lost. It causes decreases in brain volume [46][47]. The consequences of this condition manifest in cognitive and neurological problems. Atrophy can be generalized or focal. Focal cerebral atrophy and the corresponding damage affect a particular area of the brain tissue. This type of atrophy can manifest in the corresponding functional impairment of the concerned area of the brain [48][49]. Decreases of brain volume can usually be identified by computed tomography (CT) and magnetic resonance imaging (MRI). Radiological examination may show changes in the brain tissue that are closely related to cerebral atrophy. CT and MRI are equally able to demonstrate cortical atrophy, but MRI is more sensitive to the detection of some types of atrophy, such as focal atrophic changes in the nuclei [50][51][52]. A prospective follow-up study published by Nitkunan et al. showed that brain tissue volume is decreased in patients with cerebral small vessel disease with respect to normal aging subjects. Additionally, this atrophy was associated with cognition decline in 1-year follow-up [53]. Leukoaraiosis research works have proven that decreased brain tissue volume is associated with and facilitates cognitive decline. Brain atrophy due to cerebral small vessel disease is independently related to longitudinal cognitive decline [50]. The size of the white matter located in periventricular and subcortical brain tissue and the number of lacunar infarcts have been associated with the severity of brain atrophy in MRI examination [51][54][55].

Some degree of cerebral atrophy occurs naturally with age. This also applies to many pathological conditions, such as epilepsy, traumatic brain injuries, strokes, multiple sclerosis, Huntington's disease and cerebral palsy [56][57][58]. An association has been shown between cerebral cortex atrophy and drug and alcohol toxicity, as well as Alzheimer's disease (AD) [59][60]. A large number of studies have confirmed that cerebral atrophy is the most significant morphological characteristic of AD [61][62][63][64].

### 4.2. Leukoaraiosis and White Matter Hyperintensities

The term leukoaraiosis was introduced in 1987 by Hachinski, Potter and Merskey to describe bilateral periventricular hypodense areas of white matter seen in CT scans, mostly in the elderly population [65]. It roughly corresponds with white matter hyperintensities (WMH), defined as disseminated regions of white matter changes that are hyperintense in T2-weighted findings and FLAIR in MRI images, predominantly around the ventricles and subcortically. Histologically, the atrophy of axons, as well as a decreased quantity of myelin, is observed. This could be the result of an insufficient blood supply to the deep portions of white matter due to vascular pathology [66][67][68]. Makedonov et al. report that the perfusion of white matter hyperintensities (WMHs), as assessed with SPECT and MRI, is lower than the perfusion of normal-appearing white matter [69]. Other researchers point to an impairment of lymphatic drainage as the suspected mechanism rather than an infarction, because no foamy macrophages are present [70]. In patients with beta-amyloid deposits in the basement membranes of arterioles, the interstitial fluid cannot be sufficiently reabsorbed [71]. White matter hyperintensities can be found in 20% of adults in their sixties and in up to 94% in the population of octogenarians [72][73]. They are a common finding in asymptomatic patients; however, the prevalence is higher in the population affected by AD [74][75]. Likewise, patients with cardiovascular risk factors and symptomatic cerebrovascular disease are more likely to develop WMHs [76]. This has clinical implications, as shown in the Perindopril Protection Against Recurrent Stroke Study, where the WMH volume was successfully reduced after 36 months of treatment with ACE inhibitor [77]. Moreover, in a meta-analysis of nine previous studies, Debette and Markus confirmed a significant association of white matter hyperintensities with incident stroke [78]. Furthermore, recent studies have demonstrated the clinical significance of WMH with regard to bladder dysfunction as well as gait and balance disorders [79].

### 4.3. Lacunar Strokes

Lacunar strokes (LSs) of the cerebrum result from the occlusion of small perforating arteries. By definition, the diameter of a lacunar stroke lesion is less than 20 mm on the axial plane [80]. They can be classified by their shape, as tubular (resulting from the occlusion of larger perforating vessels and confluence of lesions) or oval, and by their size, which can

be as large as 15–20 mm and as small as 0–14 mm [81]. They comprise around 20% of ischemic strokes [82]. The clinical lacunar syndromes are pure motor stroke, pure sensory stroke, mixed sensorimotor stroke, ataxic hemiparesis and dysarthria/clumsy hand. Very often silent, they are found in 20–50% of elderly people [83]. Hypertension and diabetes mellitus have been established as important risk factors [84][85]. Family history data analysis suggests a hereditary predisposition for lacunar stroke [86]. Large artery abnormalities are often observed in LS, and the possibility of artery-to-artery embolism has been indicated, as shown in a study associating calcifications in the carotid siphon and silent LS [87]. Moreover, CSVD and its sequelae LS are observed to co-exist with abnormalities in small vessels of other organs, including kidneys and retina [88][89]. An important pathological mechanism is endothelial dysfunction leading to the vasoconstriction, inflammation and proliferation of the affected vessels. The circulating markers of endothelial activation, namely intercellular adhesion molecule-1 (ICAM) and thrombomodulin, are elevated in patients with LS as compared with age-matched controls [90]. Furthermore, the LS areas show increased brain–blood barrier permeability, which appears as white matter hyperintensities on MRIs. Lacunar stroke is associated with a lower rate of motor disability and urinary incontinence than stroke due to large-vessel occlusion in anterior or posterior cerebral circulation or hemorrhagic stroke. Similarly, depression is more common in survivors of large-vessel disease (52%) than in patients affected by a lacunar stroke [91]. However, intellectual disability is a serious consequence of this type of stroke, as it is often a manifestation of an underlying diffused condition of cerebral vessels. In total, 11–23% of patients with lacunar stroke will develop dementia [92][93], and the risk increases with recurrent lacunar events [94].

## 5. Conclusions

CSVD is a complex group of diseases associated with cerebrovascular architecture disorders. Their pathogenesis is very complex and varies depending on the specific unit. In most cases, they are associated with amyloid angiopathy or arteriosclerosis, but in some contingencies, genetic considerations may also play an important role. As demonstrated in recent years, the manifestation of CVSD can be of great importance in the diagnosis of patients with cognitive impairment. Genetic considerations also play a similar role in vascular diseases such as stroke. A thorough understanding of the role and ethology of cerebral small vessel disease can allow for the more careful monitoring of these groups of patients and the implementation of measures that will prevent relapse or acceleration of the progression of the disease. Developing an accurate knowledge of the meaning and full characteristics of these issues requires further research.

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