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The impact of cerebrovascular aging on vascular cognitive impairment and dementia

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Abstract

As human life expectancy rises, the aged population will increase. Aging is accompanied by changes in tissue structure, often resulting in functional decline. For example, aging within blood vessels contributes to a decrease in blood flow to important organs, potentially leading to organ atrophy and loss of function. In the central nervous system, cerebral vascular aging can lead to loss of the integrity of the blood-brain barrier, eventually resulting in cognitive and sensorimotor decline. One of the major of types of cognitive dysfunction due to chronic cerebral hypoperfusion is vascular cognitive impairment and dementia (VCID). In spite of recent progress in clinical and experimental VCID research, our understanding of vascular contributions to the pathogenesis of VCID is still very limited. In this review, we summarize recent findings on VCID, with a focus on vascular age-related pathologies and their contribution to the development of this condition.

Keywords

blood-brain barrier; hypoperfusion; vascular aging; white matter

Introduction

Age-related dementia is an irreversible condition with remarkable progressive cognitive decline. Each year, there are 7.7 million new dementia diagnoses (Iadecola, 2013). In the United States, the financial burden of dementia has already surpassed that of cancer and heart disease (Hurd et al., 2013). Vascular cognitive impairment and dementia (VCID) accounts for at least 20% cases of dementia, being second only to Alzheimer's disease (AD).

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As with AD, the incidence and severity of VCID is recognized as an urgent public health crisis (Gorelick et al., 2011). The risk for VCID rises with age, doubling every ~5.3 years (Jorm and Jolley, 1998). Thus, the prevalence of VCID is expected to increase exponentially with the aging of the US population.

VCID is a type of cognitive disorder induced by vascular abnormalities. The major hemodynamic alteration in this condition is a chronic and significant decrease in cerebral blood flow (CBF) (Sabayan et al., 2012; Scheel et al., 1999). Diverse types of pathology have been reported in VCID, including atherosclerosis, arteriolosclerosis, infarcts, white matter (WM) changes, and microbleeds. Despite much scientific progress in VCID research during the past few decades, many controversies and unanswered questions still remain (T O'Brien and Thomas, 2015). In this review, we will describe the impact of vascular aging on cerebrovascular function and the contribution of vasculopathy to cognitive impairment and dementia.

1. Cerebrovascular biology and aging

The brain vasculature consists of two blood supply systems. The major one of these is the internal carotid artery system, which carries approximately 70% of total CBF. The second is the vertebral artery system, which accounts for 30% of total CBF. These two systems converge to form the Willis circle, from which the main cerebral arteries branch out (Fig. 1A). A dense network of arterioles (Fig. 1B) is formed within the pia mater before penetration into the cortex (Willie et al., 2014b). The deeper WM is irrigated by long branches of the cerebral vascular supply, and is therefore more vulnerable to ischemic damage (Iadecola, 2013). The pial arterioles are generally considered to be the key regulators of CBF. The neurovascular unit (NVU) is a defined structure formed within brain tissue composed of the cerebral microvascular endothelium, astrocyte endfeet, pericytes, neurons, and extracellular matrix (Fig. 1C). During the process of aging, the cerebral vasculature and other components of the NVU undergo multiple changes that predispose the brain to neurovascular diseases, including VCID.

1.1 Specialized features of the cerebral vessels

Like all other vessels, cerebral vessels permit the diffusion of gas, form a physical barrier, act as a gatekeeper and participant in inflammatory process, and promote or prevent thrombosis under special circumstances (Hainsworth et al., 2015). In addition to these conventional properties shared by all vessels, cerebral vessels also exhibit some specialized functions.

The leading structural feature of cerebral vessels is the formation of a blood-brain barrier (BBB). The BBB is composed of tight junctions (TJ) and adherens junctions between endothelial cells, as well as other cellular components, such as the basal membrane, pericytes, and astrocyte endfeet (Fig. 1C) (Abbott et al., 2010). As the major interface between the blood and the neural environment, the BBB prevents harmful molecules from entering the brain tissue from the circulation. Multiple studies have reported increased BBB permeability in dementia, which contributes to neurodegeneration and functional decline

(Alafuzoff et al., 1987; Farrall and Wardlaw, 2009; Schreiber et al., 2013; Skoog et al., 1998; Zlokovic, 2008).

Cerebral vessels also play an active role in transporting specific molecules between the blood and brain tissue. Even glucose—the critical fuel for brain metabolism—is unable to enter the brain without the facilitation of transport proteins located in the endothelial luminal membrane (Hainsworth et al., 2015). This transport capacity of the cerebral endothelium is supported by a unique transcriptional profile, with overexpression of specific transporter genes compared to other types of vessels in the periphery (Demarest et al., 2012; Enerson and Drewes, 2006; Macdonald et al., 2010; Ohtsuki et al., 2014). These genes encode carrier-mediated transporters, active efflux transporters, or receptor-mediated transporters (Pardridge, 2005). Cerebral vessels continuously scan the contents of circulating blood, actively select beneficial materials, and facilitate their entry into the brain (mainly via transporters), while simultaneously blocking the passage of detrimental materials. Thus, neuronal function and survival both rely on the structural and functional integrity of cerebral vessels. In addition, brain vessels play active roles in removing neurotoxic molecules from the interstitial fluid, including amyloid-β (Aβ) (Zlokovic, 2011). Disturbance of the normal cerebral vasculature not only reduces the supply of oxygen and nutrients, but also results in the accumulation and deposition of harmful molecules in the brain.

Another distinct feature of cerebral vessels is their participation in the regulation of CBF. Major arteries and small arterioles, and even the capillaries contribute to some degree to regulation of CBF (Argaw et al., 2009; Baumbach and Heistad, 1988). This function is based on a high sensitivity to carbon dioxide (CO_2), which is unique to cerebral vasculature (Ainslie et al., 2005), and is carried out by vascular smooth muscle cells in the arterial and arteriole walls (Fig. 1A), as well as pericytes within the NVU (Fig. 1C), due to their contractile properties (Hall et al., 2014). Accounting for only 2% of total body weight, the cerebral circulation disproportionately carries about 12-20% of cardiac output, and consumes 20-25% of total oxygen and glucose (Williams and Leggett, 1989). This disproportionate distribution indicates that the brain is the most critical organ, consuming large amounts of the blood supply and with superior sensitivity to alterations in CBF alteration. Decreases in CBF therefore contribute to the pathogenesis of VCID (De Vis et al., 2015; del Ser et al., 1990; Scheel et al., 1999; Schuff et al., 2009).

The blood flow of the WM is supplied by long, penetrating arterioles that lack anastomotic branches (Blinder et al., 2013). In addition, the WM receives less blood flow—only about two thirds of the flow in grey matter (Harris and Attwell, 2012). This difference probably reflects the fewer numbers of synapses in WM, based on the observation that the brain uses most of the available energy to supply ionic pumps that maintain the ionic gradients for proper synaptic activity (Harris et al., 2012). Therefore, these vascular features render WM prone to injury in ischemia and during energy deficiency. In addition, the deep WM and basal ganglia are irrigated by arterioles arising directly from the circle of Willis and its proximal branches, which are more susceptible to mechanical stress imposed by hypertension and arterial stiffness (Scuteri et al., 2011).

1.2 Mechanisms of CBF regulation

Mechanisms of CBF regulation can be classified into three broad categories: (1) metabolic regulation of CBF, (2) cerebral autoregulation, and (3) autonomic regulation of CBF.

1.2.1 Metabolic regulation—A significant increase in the pressure of arterial carbon dioxide ($PaCO_2$) leads to vascular dilation and increases in CBF. As mentioned previously, the entire cerebral vasculature is highly sensitive to $PaCO_2$ throughout large arteries, ranging from the internal carotid arteries and vertebral arteries (Willie et al., 2012), intracranial arteries (Giller et al., 1993; Willie et al., 2011; Willie et al., 2014a), to the small pial arterioles (Wolff and Lennox, 1930), and even the capillaries of the parenchyma (Binks et al., 2008; Mandell et al., 2008; Nöth et al., 2008; Piechnik et al., 2008). Among these structures, the pial arterioles are thought to be the major site of resistance modulation (Fig. 1B). It is worth noting that some cerebral vessels such as the pial arterioles also respond to metabolic materials in the cerebrospinal fluid (CSF) (Willie et al., 2014b) as they are anatomically immersed in CSF in the subarachnoid space. Remarkably, pial arteries can dilate up to 40% upon an increase of CO_2 in both the blood and CSF (Kontos et al., 1977; Wolff and Lennox, 1930).

1.2.2. Cerebral autoregulation—Cerebral autoregulation functions to buffer CBF in response to blood pressure. It was previously widely believed that ‘in all physiological conditions, a rise in arterial pressure accelerates the CBF, and a fall slackens it (Bayliss et al., 1895)’. However, this concept was revised by Lassen and colleagues (Lassen, 1959). When these authors graphed average blood pressure against CBF, a plateau region emerged wherein the CBF appears to remain constant despite a wide range in blood pressure (60-150 mmHg). These results were based on between-subject measurements in different patients with various diseases. In 2012, Tan and colleagues conducted a within-subject analysis of 43 healthy volunteers, where CBF and blood pressure were measured simultaneously. They demonstrated that minor fluctuations in the plateau region remained within 10 mmHg, which suggests that CBF has effective buffering capacity (Tan, 2012). Aging-related hypertension and increased pulsatility disrupt normal cerebral autoregulation by affecting the function of baroceptors (Ogawa et al., 1996) and subject the aging brain to hypoperfusion (van Beek et al., 2008). This may increase vulnerability to age-related pathologies such as neurodegenerative disorders.

1.2.3 Autonomic regulation of CBF—The entire cerebral vasculature is innervated by sympathetic and parasympathetic fibers. Three layers of nerve plexi have been described. The most superficial is a perivascular layer arranged longitudinally and superficially to the adventitia. Within the adventitia, there is a dense perivascular plexus. And a deep perivascular plexus extends along the transverse axis at the adventitial-medial border (Tan, 2012). In general, excitation in the sympathetic nervous system decreases CBF and excitation in parasympathetic nerves increases CBF (Ainslie, 2009; Cassaglia et al., 2008; Mayhan et al., 1987; Tzeng et al., 2010).

1.3 Cerebrovascular aging and mechanisms

Healthy cerebrovascular function is defined as the coordinated regulation of CBF so that it meets neuronal requirements (Bolduc et al., 2013). Aging leads to complex vascular phenotypic changes that render the brain prone to diseases, especially VCID, regardless of the existence of traditional risk factors (Ungvari et al., 2010). Multiple pathophysiological processes participate in accelerated aging and aging-related cerebrovascular disorders, as described further below.

1.3.1 Arterial stiffness—Arterial stiffness is a major feature of vascular aging. The stiffness of large conduit arteries increases both pulse wave velocity and pulse pressure, leading to an increase in systolic pressure and decrease in diastolic pressure. Alterations in blood flow dynamics result in the expression of mechanosensitive genes, which induce vascular remodeling, oxidative stress, and pro-atherogenic changes in the vascular wall (Ungvari et al., 2010). Upregulation of the renin-angiotensin system (Spinetti et al., 2004; Wang et al., 2007; Wang et al., 2005) and elevation in advanced glycation end products (Semba et al., 2009; Semba et al., 2015) also contribute to arterial wall stiffness.

1.3.2 Endothelial replicative senescence—Cellular senescence arrests the proliferation of mitotically competent cells, leading to permanent withdrawal from the cell cycle and is recognized as an example of evolutionary antagonistic pleiotropy (Campisi, 2003), preventing organs from developing cancer early in the reproductive years while promoting age-related phenotypes and pathologies (Chinta et al., 2015). In addition, senescent cells acquire a distinct phenotype known as the senescence-associated secretory phenotype and secrete multiple inflammatory cytokines, growth factors, and proteases that contribute to aging and the development of aging-related diseases (Chinta et al., 2015; Coppé et al., 2010). These detrimental factors are likely to function as paracrine mediators, altering neighboring cells and modulating the internal milieu. Senescent cells are known to accumulate with age in a variety of tissues (Erusalimsky and Kurz, 2005; Herbig and Sedivy, 2006; Jeyapalan et al., 2007; KISHI, 2004). Studies on cultured endothelial cells suggest that oxidative stress is a major stimulus to induce endothelial senescence (Erusalimsky, 2009). In the aged brain, cellular senescence is associated with impaired cognition and an increase in pro-inflammatory cytokines such as interleukin (IL)-1β and IL-6 (Bachstetter et al., 2011). However, the relationship between cellular senescence and dementia remains poorly understood.

1.3.3 Microvascular rarefaction—Rarefaction of the microvasculature has been reported in some regions of the brain, especially the hippocampus and the residual vessels show structural alterations that are associated with the development of VCID (Riddle et al., 2003; Sonntag et al., 1997). The causes for microvascular rarefaction are not fully understood. A higher rate of endothelial apoptosis is observed in aged rodents (Csiszar et al., 2007b; Csiszar et al., 2004; Pearson et al., 2008) and non-human primates (Asai et al., 2000). Oxidative stress and chronic inflammation may contribute to endothelial apoptosis. Another reason for microvascular rarefaction may be related to circulating endothelial progenitor cells. Dysfunction in and decreased numbers of circulating endothelial progenitor cells have been reported with aging (Chang et al., 2007; Heiss et al., 2005; Zhang et al.,

2009), and this is associated with WM changes and cognitive impairments (Hajjar et al., 2016; Hayakawa et al., 2013).

1.3.4 Narrowing of the vascular lumen—The major causes of luminal narrowing are atherosclerosis in large vessels and arteriosclerosis in small vessels, characterized by deposition of atherosclerotic plaques (Jellinger, 2008, 2013; Yurdagul et al., 2016). The accumulation of toxic proteins in the vessel walls also causes narrowing of the vascular lumen. Examples of such proteins include 1) mutant Notch3 in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and 2) high-temperature requirement A serine peptidase 1 (HTRA1) in cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (Fukutake, 2011; Hara et al., 2009; Henshall et al., 2015; Joutel et al., 1996). Luminal narrowing causes chronic cerebral hypoperfusion, ischemia, and oxidative stress, eventually leading to cognitive impairments and dementia.

1.3.5 Oxidative stress in inflammation—Although the mechanisms underlying vascular aging are not fully understood, oxidative stress and inflammation may play important roles. Excessive oxidative stress contributes to vascular aging in both laboratory animals (Csiszar et al., 2007a; Hamilton et al., 2001; Sun et al., 2004; Ungvari et al., 2010; Van Der Loo et al., 2000) and humans (Donato et al., 2007; Jablonski et al., 2007), and this may increase the risk of vascular diseases such as stroke, VCID, and coronary heart disease. The age-related increase in reactive oxygen species (ROS) may at least partly be attributed to the increased activity of nicotinamide adenine dinucleotide phosphate-oxidase in vessel walls (Adler et al., 2003; Csiszar et al., 2007a; Donato et al., 2007; Jacobson et al., 2007; Van Der Loo et al., 2000). Nitric oxide (NO) is a critical vasodilation factor that contributes to CBF regulation; it can be inactivated by high levels of superoxides, resulting in significant cerebral vasomotor dysfunction (Ungvari et al., 2008). In addition to regulation of the CBF, NO also confers vascular protective effects, including inhibition of platelet aggregation, inhibition of endothelial apoptosis, preservation of endothelial progenitor cells, and anti-inflammatory properties (Ungvari et al., 2010). These benefits of NO are all compromised by ROS. Furthermore, proxynitrite, the oxidative product of NO, causes severe cytotoxicity, leading to cellular death not only in cerebral vessels, but other cell types as well, including neurons (Pacher et al., 2007).

Increasing evidence suggests that mitochondrial oxidative stress plays an important role in aging-induced cerebral vascular dysfunction (Springo et al., 2015). Mitochondrial-derived H_2O_2 activates nuclear factor (NF)-κB, leading to a pro-inflammatory shift in endothelial gene profiles (Ungvari et al., 2007). In addition, oxidative stress damages mitochondrial DNA, further contributing to the pathogenesis of dementia (Bonanni et al., 2015; Coppedè and Migliore, 2015).

Both experimental and clinical data demonstrate that aging is associated with continuously low-grade inflammation, rendering the vasculature vulnerable to atherosclerosis, the major vasculopathy in VCID (Csiszar et al., 2008; Franceschi et al., 2000; Nilsson et al., 2015; T O'Brien and Thomas, 2015). As discussed above, oxidative stress induces vascular inflammation in experimental aging models (Csiszar et al., 2003, 2004; Pearson et al., 2008;

Ungvari et al., 2007; Wang et al., 2007). In humans, diverse inflammatory factors are positively correlated with age, and this is independent of conventional risk factors (Bruunsgaard et al., 2000; Miles et al., 2008). These inflammatory factors include, tumor necrosis factor (TNF)-α, IL-6, and IL-1β, which are associated with increased risk of developing VCID (Zuliani et al., 2007). High levels of pro-inflammatory factors contribute to a pro-inflammatory microenvironment, which facilitates vascular dysfunction and promotes endothelial apoptosis, mainly through activation of NF-κB (Arenas et al., 2006; Donato et al., 2008; Donato et al., 2007; Ungvari et al., 2007; Zou et al., 2006).

2. Vascular pathophysiology underlying VCID—how does vascular aging lead to neural disorders?

Decreased CBF is the major cerebral hemodynamic alteration in VCID (Sabayan et al., 2012; Scheel et al., 1999). Diverse vascular and cerebral pathologies have been reported in VCID, including atherosclerosis, arteriolosclerosis, infarcts, WM changes, and microbleeds. In this section, we will classify and describe vasculopathies associated with VCID.

2.1. Diverse cerebrovascular pathologies underlying VCID

As summarized in Fig. 2, multiple cerebrovascular pathologies can cause VCID. Pathologies that cause reduction in global CBF such as atherosclerosis and arterial stenosis can induce VCID. If the CBF reduction is severe and persistent, stroke and infarcts may develop (Moskowitz et al., 2010).

The most prevalent vascular lesions associated with VCID are small vessel diseases (SVDs) (Hainsworth et al., 2015; Jellinger, 2013; Pantoni, 2010). Diverse vascular pathologies can cause SVDs, which are composed of atherosclerotic plaques in small vessels, deposition of hyaline in the vascular wall (lipohyalinosis), and vessel wall fibrosis, resulting in microvascular stiffening and distortion (arteriolosclerosis) (Fig. 2) (Thal et al., 2012).

Deposition of Aβ in cerebral vessels, termed cerebral amyloid angiopathy (CAA), is associated with VCID. The major risk factor for CAA is advanced age (Charidimou et al., 2012). The amyloid accumulation occurs in the media and adventitia, resulting in degeneration of vascular smooth muscle cells and pericytes (Thal et al., 2012). Both ischemic and hemorrhagic lesions can be observed in CAA. Another type of SVD that leads to VCID is CADASIL, in which the vascular lesions are related to accumulation of granular osmiophilic material that contains the mutant Notch 3 protein (Cognat et al., 2014; Joutel et al., 1996; Paquet et al., 2010).

2.2. Vascular gray matter injuries

Selective neuronal death and cerebral infarction are the major pathologies in gray matter injury, and their usual cause is cerebral ischemia (Fig. 2). Selective neuronal death occurs in vulnerable regions such as hippocampal CA1 and layer 3 and 5 of the cerebral cortex (Won et al., 2012; Zhang et al., 2013). Reductions in global CBF such as those caused by heart disease or carotid artery stenosis/occlusion can induce neuronal death and cognitive impairments (Marshall et al., 2012). There is general consensus that the cognitive

impairments in this case are caused by cumulative brain tissue damage (Gelber et al., 2012; Sacco et al., 2013). Cerebral infarction is typically caused by occlusion of arterioles and consequent acute ischemia. If the lesion is located in regions responsible for cognitive function, such as the frontal lobe and thalamus, it will induce a “strategic” infarct, leading to cognitive dysfunction (Lanna et al., 2008).

2.3. Vascular WM injuries

Myelinated WM tracts are responsible for long-range connectivity, inter-hemispheric synchronization, neurotrophic effects through axonal transport, neuroplasticity, and learning. Disruption of the WM has profound effects on the precision of information transfer (Nave, 2010). WM lesions are associated with global reduction of CBF and cardiovascular risk factors, especially hypertension, diabetes, smoking, and hyperlipidemia (Burton et al., 2004; Polvikoski et al., 2010; Udaka et al., 2002; Yoshizaki et al., 2008). Compared to gray matter injuries, the mechanisms underlying vascular WM injuries are more complex, and multiple vascular-oriented pathogenic factors collaborate with each other to contribute to its pathogenesis (Fig. 3).

2.3.1. BBB disruption—A meta-analysis of BBB permeability in 1953 individuals demonstrated that BBB permeability increases with aging, even in healthy humans (Farrall and Wardlaw, 2009). Furthermore, patients with AD and leukoaraiosis exhibit even greater BBB dysfunction. The leading mechanism responsible for BBB disruption is the excessive production of matrix metalloproteinases (MMPs), due to chronic hypoxia and inflammation induced by age-related vascular changes. MMPs facilitate the degradation of TJ proteins and the basement membrane. In addition, even normal aging can lead to pericyte loss, which results in further BBB disruption and microvascular degeneration (Bell et al., 2010).

BBB breakdown leads to the accumulation of neurotoxic materials in cerebral vessels or the brain parenchyma. For example, the accumulation of plasma proteins such as immunoglobulin and albumin can lead to brain edema and suppress capillary blood flow (Bell et al., 2010), whereas thrombin causes neurotoxicity and cognitive impairments (Mhatre et al., 2004). Furthermore, plasmin has been shown to catalyze the degradation of laminin (Chen and Strickland, 1997), and fibrin can accelerate neurovascular damage (Paul et al., 2007). In extreme cases, red blood cells leak into brain tissue, resulting in the deposition of hemoglobin-derived neurotoxic molecules such as iron, which contributes to ROS generation through Fenton chemistry (Zhong et al., 2008).

2.3.2. Hypoxia and hypoperfusion—WM is more vulnerable to CBF reduction compared to gray matter due to reduced vascular perfusion. This increased vulnerability is exemplified by the ‘intracerebral steal’ phenomenon, whereby hypercapnia or vasodilators decrease CBF in the periventricular WM due to vasodilation of upstream vessels that ‘steal’ the blood flow of the WM (Mandell et al., 2008). Systemic vascular aging such as hypertension and stiffness impair cerebrovascular autoregulation and decrease resting CBF, and are strong predictors of WM lesions (Jennings et al., 2005; Matsushita et al., 1994; Tarumi et al., 2011; Webb et al., 2012).

A decrease in CBF also exists in otherwise normal-appearing WM, suggesting that hypoperfusion precedes cognitive dysfunction (O'Sullivan et al., 2002). Mild hypoperfusion can impair protein synthesis, which is necessary for synaptic plasticity during learning and memory consolidation (Iadecola, 2004). Severe hypoperfusion causes failure to form action potentials (Kalaria, 2010) and alters acid-base balance and electrolyte concentrations, inducing neuronal/axonal edema and the accumulation of neurotoxic proteins (Aβ and glutamate), all of which lead to WM injury (Kalaria, 2010). Multiple studies have shown that ischemia-hypoxia increase the activity of two critical enzymes for Aβ production: β-secretase and γ-secretase (Li et al., 2009; Sun et al., 2006), and decreased levels of the Aβ degrading enzyme neprilysin (Wang et al., 2011).

2.3.3. Oxidative stress and neuroinflammation—Oxidative stress and chronic neuroinflammation may be present within WM lesions and are strongly associated with VCID, as indicated by the elevation of oxidative markers and inflammatory factors in this condition (Morrison et al., 2010; Yates et al., 2012; Zhang et al., 2014). In addition, activated microglia and astrocytes are present in WM lesions, which might exacerbate oxidative stress (Simpson et al., 2007). Therapeutic scavenging of ROS and anti-inflammatory approaches have been used to suppress inflammation and attenuate WM injuries in rodent models (Ma et al., 2015; Ueno et al., 2009; Wakita et al., 2008).

2.3.4. Disturbance of trophic coupling—Within the NVU (Fig. 1C), endothelial cells play a supportive role by secreting multiple growth factors. The most well studied of these are vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) (Nakahashi et al., 2000). VEGF has diverse functions, including angiogenesis, axonal guidance, and the migration of oligodendrocytes and oligodendrocyte precursor cells (OPCs) (Carmeliet and de Almodovar, 2013; Quaegebeur et al., 2011). In the adult brain, BDNF guides the migration of neuroblasts along blood vessels (Snapyan et al., 2009), and promotes the proliferation and survival of oligodendrocytes (Arai and Lo, 2009). Aging induces endothelial apoptosis (Csiszar et al., 2007b; Csiszar et al., 2004; Pearson et al., 2008) and microvascular rarefaction (Riddle et al., 2003; Sonntag et al., 1997), thereby impairing the normal supportive function of the vessel walls, which contributes to the malfunction of neurons and oligodendrocytes.

2.3.5. Demyelination and failure of remyelination—Hypoperfusion and BBB breakdown, together with an oxidative and inflammatory milieu, can lead to demyelination (Iadecola, 2004; Iadecola, 2013). Demyelination slows down action potentials and can lead to axonal loss (Fig. 3) (Franklin and Ffrench-Constant, 2008). This may be attributed to a decrease in axonal supportive factors derived from oligodendrocytes, such as insulin-like growth factor (Wilkins et al., 2003). Demyelination also exposes the axon to a deleterious microenvironment in WM, as the interstitial space is then filled with cytokines and ROS.

In damaged WM, there may be compensatory attempts to remyelinate axons, but most of these efforts fail (Franklin and Ffrench-Constant, 2008; Jonsson et al., 2012). The following factors are responsible for this failure: 1) Oligodendrocytes and OPCs are extremely vulnerable to hypoxia and oxidative stress in ischemic WM (Back et al., 2011; Fernando et al., 2006) (French et al., 2009); 2) withdrawal of trophic support from endothelial cells

reduces remyelination capacity (Arai and Lo, 2009); 3) failure of OPC maturation prevents myelination. These factors may be the result of oxidative stress (French et al., 2009), dysregulation of Wnt signal transduction (Fancy et al., 2011), and excessive hyaluronan cleavage products (Preston et al., 2013). Finally, OPCs can also produce MMP9 and induce early BBB breakdown (Seo et al., 2013).

3. Age-related VCID

3.1 Risk factors of VCID

Several factors increase the risk of VCID and can be classified into two categories. The first category contributes to or accelerates vascular aging, and includes hypertension, smoking, heart disease, diabetes, obesity, hypercholesterolemia and hyperhomocysteinemia (de Bruijn and Ikram, 2014; Jackson and Sudlow, 2006; Kalaria, 2010). The second category is specific to the brain and increases the risk of cognitive impairments. It includes aging, female gender, and lower education (Pendlebury and Rothwell, 2009; Wiesmann et al., 2013). Stroke and depression also increase the risk of VCID (Diniz et al., 2013; Thomas et al., 2004).

3.2 Subtypes of VCID

According to a most widely applied VCID classification scheme, seven subtypes with specific imaging changes have been described (T O'Brien and Thomas, 2015). (1) Multi-infarct dementia: multiple cortical infarcts; (2) small vessel dementia (subcortical vascular dementia): lacunes and extensive WM lesions; (3) strategic infarct dementia: infarct in strategic locations such as the thalamus; (4) hypoperfusion dementia: watershed infarcts, WM lesions; (5) hemorrhagic dementia: hemorrhagic changes, which may or may not be associated with amyloid angiopathy; (6) hereditary vascular dementia (CADASIL and CARASIL): multiple lacunes and WM lesions, with disruption of temporal lobe WM; (7) AD with cardiovascular diseases: combination of vascular changes and atrophy, mainly affecting the medial temporal lobe.

In the current review, we classify VCID based on etiology and describe experimental models that attempt to simulate the clinical syndrome.

3.2.1. Ischemic VCID—Ischemic VCID is characterized by a reduction in CBF and accounts for the majority of VCID cases. Both large and small vessel diseases contribute to ischemic VCID. In large vessel diseases, reduced CBF leads to cerebral hypoperfusion, which further induces ischemic injury and oxidative stress in gray and white matters. Loss of neurons and neuronal dysfunction underlie severe cognitive abnormalities. In addition, WM injury is observed in VCID due to large vessel diseases, which can present as diffuse WM rarefaction, vacuolation, demyelination, axonal atrophy and loss, and lacunar infarcts multiple infarcts, or enlarged perivascular spaces (Fig. 2) (Fernando et al., 2006; Liu and Zhang, 2012; Shibata et al., 2004; Yoshizaki et al., 2008). These WM alterations can occur in isolation or, more commonly, coexist within the same brain (T O'Brien and Thomas, 2015).

Accumulating data suggest that SVDs cause the majority of VCID cases (Erkinjuntti et al., 2004; Raz et al., 2016; Roman et al., 2010). The brain pathologies in SVDs include hyalinization of vessels, expansion of the perivascular space, and pallor of adjacent perivascular myelin, with astrocytic gliosis (Kalaria, 2012). BBB dysfunction is often seen as an early change in SVDs, and exhibits increased permeability to inflammatory factors such as IL-1, IL-6, and TNFα (Iemolo et al., 2009; Reuter et al., 2015), which penetrate the brain and exacerbate the encephalopathy associated with edema (Chen et al., 2011; Park et al., 2010). The neuropathology of SVD is driven by severe stenosis and microvessel occlusion, which induces WM ischemia and multiple lacunar infarcts in subcortical regions (Raz et al., 2016).

SVDs are a group of heterogeneous diseases, and based on etiology, are generally classified as sporadic or hereditary. Sporadic SVDs are age-related diseases, with progressive arteriopathy/arteriolopathy, subcortical infarcts, and WM disease (Craggs et al., 2014), and with hypertension as a major risk factor. Binswanger's disease, or subcortical leukoencephalopathy, is a type of SVD associated with typical arteriosclerotic leukoencephalopathy within deep WM (Cai et al., 2015). Arterial hardening leads to luminal narrowing or occlusion, resulting in chronic ischemia and multiple infarcts within the WM (Rosenberg et al., 2014). MMPs play an important role in the pathogenesis of Binswanger's disease, due to their contribution to the opening of the BBB, demyelination, and oligodendrocyte degeneration (Rosenberg, 2016).

Hereditary SVDs include CADASIL and CARASIL. CADASIL is characterized by mutations in the Notch3 gene (Joutel et al., 1996). The Notch3 pathway plays an important role in cell growth, apoptosis, and differentiation (Bianchi et al., 2006; Henshall et al., 2015). Mutations in Notch3 lead to the accumulation of granular osmiophilic materials in vessel walls and the apoptosis of vascular smooth muscle cells, profoundly impacting vessel contraction and CBF regulation (Henshall et al., 2015). Aβ1-42 levels are elevated in CADASIL patients, which may also contribute to further pathogenesis (Paquet et al., 2010). CARASIL is associated with mutations in the HATRA1 gene, which lead to a decrease in protease activity and failure to repress TGF-β family signaling. Hyperactivity of TGF-β signaling contributes to vascular fibrosis and a decline in CBF (Hara et al., 2009; Lan et al., 2013).

3.2.2. Hemorrhagic VCID—Both major and minor cerebral hemorrhages lead to increased risk of developing VCID. Intracerebral hemorrhages (ICH) account for ~10–20% of all strokes, and increase morbidity and mortality (Feigin et al., 2009; Mozaffarian et al., 2016). As in ischemic stroke, cognitive decline in ICH occurs at two different stages following stroke: the acute-subacute stage and the chronic stage. Traditional vascular risk factors contribute to ICH, with hypertension being the most significant (Ferket et al., 2014; O'Donnell et al., 2010). Indeed, hypertension increases the risk of ICH by two fold (Jackson and Sudlow, 2006). As one might expect, the underlying pathologies correlate with specific anatomical locations of the hemorrhage (Fazekas et al., 1999; Woo et al., 2002; Xiong et al., 2016). ICH is thought to be the result of SVD in up to 85% of hemorrhagic stroke patients, due to hypertensive arteriopathy-induced rupture of small arterioles in non-lobar regions, such as the basal ganglia, thalamus, cerebellum and brainstem (Kremer et al., 2015).

However, a fairly large proportion of lobar ICHs result from rupture of small and medium-sized arteries in the elderly, due to accumulation of amyloid-beta in both cortical blood vessels and leptomeninges (Kremer et al., 2015). Consistent with this view, CAA accounts for the majority of lobar ICH in the elderly (Greenberg, 1998; Hernandez-Guillamon et al., 2012; Knudsen et al., 2001), and is significantly associated with lobar and cerebellar ICH but not with deep ICH (Samarasekera et al., 2012; Yamada, 2015).

Cerebral microbleeds (CMBs), defined as chronic hemorrhagic microvascular lesions or microangiopathy in the brain, also contribute to VCID. Although traditionally considered to be clinically silent (Greenberg et al., 2009; Lei et al., 2013), CMBs are present in 17% to 46% of patients with cognitive impairments (Cordonnier et al., 2006). Thus, CMBs are regarded as an independent factor for cognitive deficits (Lei et al., 2013; Miwa et al., 2014; Pasquini et al., 2016). As one might expect, CMBs are also related to traditional vascular risk factors (Seshadri et al., 2004). For example, an association of deep CMBs with hypertensive vasculopathy and lobar CMBs with CAA has been identified through positron emission tomography (Greenberg et al., 2009; Gurol et al., 2012; Romero et al., 2014; Wiegman et al., 2014). Histopathologic studies indicate that CMBs are related to structural angiopathy and account for hypertensive arteriopathy, vascular β-amyloid deposition, and concomitant microstructural damage of surrounding tissue (Werring et al., 2010). As in ICH, the etiology of CMBs is thought to vary depending on the topographical location of the injury. CMBs that are located in deep brain tissue are related to hypertensive vasculopathy, whereas those at the cortico-subcortical boundaries of the cerebral lobes are related to CAA (Auer and Sutherland, 2005; Greenberg et al., 2009; Vernooij et al., 2008; Werring et al., 2010).

3.2.3. Post-stroke dementia—Stroke is the second leading cause of cognitive dysfunction, and it increases the risk of cognitive impairment by five folds (Merino, 2002; Qu et al., 2015; Srikanth et al., 2003). Recent clinical studies indicate that VCID occurs in about 25-30% of elderly stroke survivors (Allan et al., 2011; Savva et al., 2010). Not only may cognitive decline occur immediately following the onset of stroke (Nakase et al., 2013; Nys et al., 2007), but progressive cognitive disorders might also set in after the acute phase has passed (Altieri et al., 2004; Douiri et al., 2013). Post-stroke dementia may encompass all types of cognitive dysfunction, and the specific symptoms depend on stroke location, type, volume, and number. As each cortical lobe controls distinct cognitive functions, stroke in regions such as the hippocampus and temporal lobe leads to acute cognitive impairments more frequently than stroke in other regions such as the occipital lobe. In addition, stroke-mediated cognitive deficits are more strongly associated with lesions that affect the dominant hemisphere (Kalaria et al., 2016). The risk factors for post-stroke dementia are multifactorial, and include advanced age, genetic traits, low educational status, stroke severity, presence of diabetes, multiple infarcts, prior transient ischemic attack or recurrent stroke, and depressive illness (Gregoire et al., 2012; Jacquin et al., 2012; Kalaria et al., 2016; Kim et al., 2012; Leys et al., 2005; Lin et al., 2003; Yang et al., 2015).

As the cognitive decline after stroke has a close relationship with the overlapping pathology of cerebrovascular disease and dementia, the mechanisms accounting for post-stroke dementia are complex (Deramecourt and Pasquier, 2014; Iadecola, 2013). Some of the most

important causes of post-stroke dementia are lesions of neuroanatomical structures and cerebral vessels (Sun et al., 2014). In post-stroke dementia, a series of events, such as energy failure, excitoxicity, calcium overload, inflammation, and oxidative stress lead to microvascular damage, vasogenic edema, BBB disruption, hemostatic activation, pro-inflammatory immune responses, and cell death in the NVU (Kalaria et al., 2016). Furthermore, neuronal death following stroke is largely attributed to a continuum of apoptosis–necrosis (Kalaria et al., 2016). These stroke-related processes subsequently impair the neurological function of the brain and contribute to cognitive decline.

WM injury is an integral part of stroke and consists of activated microglia, astrocytosis, shrunken oligodendrocytes, myelin rarefaction, and axonal abnormalities and degeneration (Fernando et al., 2006; Ihara et al., 2010; Polvikoski et al., 2010). WM injury contributes to cognitive decline in stroke and cerebral SVD, and its severity is correlated with the degree of cognitive impairment (Pantoni, 2010; Sun et al., 2014). Although the pathophysiological mechanisms underlying WM lesions after stroke remain elusive, recent studies indicate that the presence and severity of WM hyperintensities on T2-weighted or FLAIR magnetic resonance images are predictive of post-stroke dementia (Burton et al., 2004; Ihle-Hansen et al., 2011; Kalaria et al., 2016; Leys et al., 2005; Sachdev et al., 2007).

CMBs are not uncommon in the general elderly population and their prevalence increases with age (Koennecke, 2006; Sveinbjornsdottir et al., 2008; Wiegman et al., 2014). CMBs are now accepted as the manifestation of cerebral small vessel pathologies, including hypertensive SVD and CAA (Poels et al., 2010; Vernooij et al., 2008; Werring et al., 2010). Higher numbers of CMBs are associated with poorer cognitive function according to numerous clinical studies (Miwa et al., 2014; Poels et al., 2012; Wiegman et al., 2014). Multiple CMBs or mixed CMBs independently indicate higher risk of post-stroke dementia (Miwa et al., 2014).

4. Animal models of VCID

Despite an impressive degree of progress in VCID research in the past several decades, the pathogenesis and underlying mechanisms of VCID remain poorly understood. In order to understand VCID at a mechanistic level, it is essential to use experimental models (Helman and Murphy, 2016; Madigan et al., 2016). In the next section, we will describe the most frequently used animal models for VCID research (Table 1).

4.1. Ischemic VCID models

4.1.1. Large vessel occlusion models—Large vessel occlusion models are achieved by occluding major cerebral arteries, such as the common carotid artery (CCA) by itself or in combination with the vertebral arteries. Depending on the number of cerebral arteries occluded, there are four types of animal models that mimic VCID induced by large vessel disorders. All of them lead to chronic, relatively mild cerebral ischemia, with significant decline in CBF (Helman and Murphy, 2016; Venkat et al., 2015).

Unilateral CCA occlusion (UCCAO): In this model, one CCA is permanently occluded, typically in mice (Yoshizaki et al., 2008). This model induces WM rarefaction and decreased

synaptic plasticity, and is accompanied by significant neuroinflammatory responses. However, the resultant neurodegeneration is relatively mild.

Two-vessel occlusion (2VO), also known as bilateral common carotid artery occlusion (BCCAO): 2 VO is induced by permanently occluding both CCAs, and is the most frequently used model of VCID (Liu and Zhang, 2012; Ma et al., 2015; Ni et al., 1995; Shibata et al., 2004; Soria et al., 2013; Wakita et al., 2002; Zhao et al., 2014). Mice cannot tolerate sudden occlusion of both CCAs. Therefore, this model is only used in rats, including spontaneously hypertensive rats (Yamaguchi et al., 1994; Yamori et al., 1976). 2VO causes chronic cerebral hypoperfusion, especially in the forebrain, leading to early BBB disruption, WM rarefaction, axonal and myelin damage, hippocampal and cortical neuron damage, as well as neuroinflammation.

Bilateral CCA stenosis (BCAS): This model is developed for VCID research in mice, and includes symmetric and asymmetric occlusion of the two CAAs. In symmetric models, microcoils (Nishio et al., 2010; Shibata et al., 2004) or ameroid constrictors (Hattori et al., 2014a; Hattori et al., 2014b) are placed around the CAAs. When ameroid constrictors are used, the CCAs will be gradually narrowed and eventually occluded around 3-4 weeks after surgery. Asymmetric BCAS is created by applying a microcoil around one CCA and an ameroid constrictor around another CCA (Hattori et al., 2015). In these models, WM lesions and rarefactions are induced in the corpus callosum, with significant inflammation, gliosis, and BBB disruption. The models are also associated with delayed hippocampal damage and atrophy.

Four-vessel occlusion (4VO): 4VO for VCID differs from a global ischemia model and is induced by a sequential three-stage occlusion of the vertebral arteries and CCAs. Both vertebral arteries are occluded, followed by occluding one CCA, and then followed by occluding another CCA, with inter-stage intervals of 7 days (Neto et al., 2005). This model induces cognitive impairments as well as neurodegeneration in the hippocampi and retina.

4.1.2. Small vessel occlusion models—To mimic SVDs, microemboli can be injected into the internal carotid artery or middle cerebral artery, which can induce multiple infarcts in the cortex and subcortical structures. The microemboli are either cholesterol crystals/microspheres, or microbeads/thrombi, or thrombus fragments, with a size range of 40–100 μm (Rapp et al., 2008; Shih et al., 2013; Venkat et al., 2015). It has been reported that the occlusion of a single penetrating vessel can lead to microinfarcts and cognitive impairments (Shih et al., 2013). Rapp and colleagues (Rapp et al., 2008) compared the effects of embolus types in the induction of infarcts, and found that the infarcts induced by cholesterol crystals are smaller than those induced by thrombus fragments of the same size, especially in subcortical tissue. With thrombus fragments, astrocytic and microglial activation were limited within the infarct sites, whereas with cholesterol crystals, microglial activation and BBB damage were widespread.

Given that CADASIL is caused by Notch3 mutations, the TgPAC-Notch3^{R169C} mouse has been introduced as a preclinical CADASIL model and is characterized by progressive, age-related cerebral WM pathology (Cognat et al., 2014). In this model, loss of oligodendrocytes

occurs before axonal injury, and the myelin damage is progressive and segmental. Intramyelinic edema is present as an early and conspicuous feature of cerebral WM changes, resulting in poor clearance of myelin debris. Another mouse model for CADASIL uses an Arg170Cys substitution in murine Notch3, mimicking the Arg169Cys mutation in CADASIL patients (Wallays et al., 2011). In this knock-in mouse model, Notch3Arg170Cys can be expressed unperturbed, allowing for direct comparison to wildtype littermates. In addition, arteriopathy develops in both the brain and peripheral sites (tail) with granular osmiophilic material deposition in blood vessels. Histological analyses of these mouse brains demonstrate many similarities with the typical features of CADASIL in human beings.

It is worth noting that these ischemic models were predominantly applied in young or middle animals in majority of the studies, and the results obtained from young animals may not reflect the impacts of cerebrovascular aging on VCID. Although the researches on cognitive decline in aged animals are common (Krause et al., 2008; Murchison et al., 2009; Bobkova et al., 2015; Gocmez et al., 2016; Smith et al., 2015), the literature on the effects of aging on ischemic VCID is very rare. In a study comparing the different effects of hypoperfusion on between young and aged rats, it is reported the aged rats showed continuous hippocampal CBF decrease, spatial memory deficiency and CA1 neuronal death, which are companied by increased astrocytic response (Dela Torre et al., 1992). A recent study shows that post-stroke cognitive impairment presents in both young and aged mice; however, aged mice demonstrate more sever memory decline. Underlying mechanisms include CBF reduction, increased myelin loss and reduced M2 phenotype of microglia/macrophage (Suenaga et al., 2015). The shared findings of these two studies are the more severe cognitive impairment and reduction of CBF in aged animals, probably due to the aging of cerebral vasculature. Apparently, more integrated and systematic researches on aged animals are needed to clarify the effect of cerebrovascular aging on VCID.

4.2 Hemorrhagic VCID models

Compared to the ischemic VCID models, hemorrhagic VCID models are difficult to establish and less frequently used. ICH models are generally induced by intraparenchymal injection of bacterial collagenase or blood (MacLellan et al., 2008). Some studies have established cognitive disorders after ICH in rats (Hartman et al., 2009; MacLellan et al., 2009), which can be recognized as hemorrhagic VCID models. However, induction of ICH in otherwise healthy animals is not necessarily representative of spontaneous ICH in humans. Thus, hypertension-related and CAA-related spontaneous ICH animal models have been introduced to mimic clinical scenarios, albeit to a limited degree.

Transgenic mice with both human renin and angiotensinogen genes may be useful to mimic chronic hypertension (Merrill et al., 1996). Based on the hypertensive model, double transgenic animals treated with a high-salt diet or N-nitro-L-arginine methyl ester develop severe hypertension with symptomatic ICH (Ahmad, 1997; Iida et al., 2005; Smeda, 1989). Furthermore, transgenic animal models are widely used in CAA-related spontaneous ICH. For example, APP23 transgenic mice contain β-amyloid precursor protein (APP) expressing human APP with the Swedish mutation (Winkler et al., 2001), Tg2576 transgenic mice

express human APP 695 with the Swedish mutation (Fisher et al., 2011), APP Dutch mice express AβDutch40 (Herzig et al., 2004), and Tg-SwDl mice harbor Swedish and vasculotropic Dutch and lowa mutations (Davis et al., 2004). All these transgenic models exhibit spontaneous ICH.

5. Summary

As a common age-related disease, VCID is attracting increasing attention due to its ever-increasing prevalence and significant economic and social burden. Age-related vascular pathology and CBF dysregulation contribute to the pathogenesis of VCID. Although several animal models and behavioral tests have been used to mimic and assess VCID, significant progress has not been made and the definition, diagnostic criteria, and treatments are still debated. Therefore, a more fruitful collaboration across basic science, translational, and clinical approaches is urgently needed to establish effective treatment strategies for VCID patients.

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Highlights

1. Cognitive impairment and dementia are age-related health burden.
2. Neurovascular aging predisposes the brain to reduced blood flow and long-term ischemic injuries, leading to VCID.
3. Diverse pathology underlies VCID, including neuronal loss and white matter injury. Microinfarcts and leukoaraiosis are common.
4. Age-related VCID can be classified into ischemic, hemorrhagic and post-stroke subtypes.

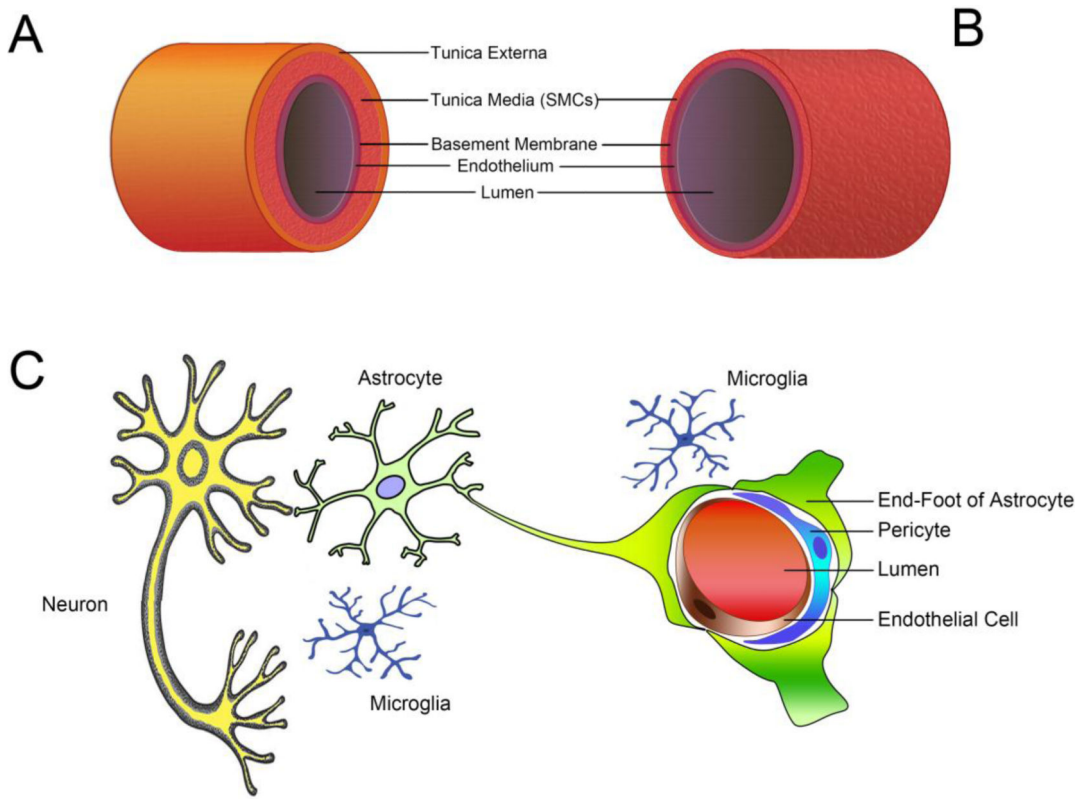

Fig. 1. Anatomical structures of the cerebral vasculature

(A) Brain artery branch from the circle of Willis. The vessel wall contains three layers. The tunica externa is composed of connective tissue and elastic fibers. The tunica media is a thick layer of smooth muscle cells that control vessel tone. In the inner layer, the tunica intima consists of a monolayer of endothelial cells that rest on the basement membrane. (B) Brain arteries branch into a dense network of arterioles within the pia mater. These arterioles lack the tunica externa but contain the thinner media layer. As the major switch that controls the CBF, these arterioles are exposed to both blood in the lumen and the CSF rushing through the subarachnoid space. (C) The structure of the NVU is unique to the brain. Pericytes are contractile cells sitting outside the endothelial monolayer. The endothelial cells and neurons are connected by astrocyte endfeet. Microglial cells migrate around the NVU. Complex cell-cell interactions exist within the NVU and are integrated to control CBF and cellular function. SMCs: smooth muscle cells.

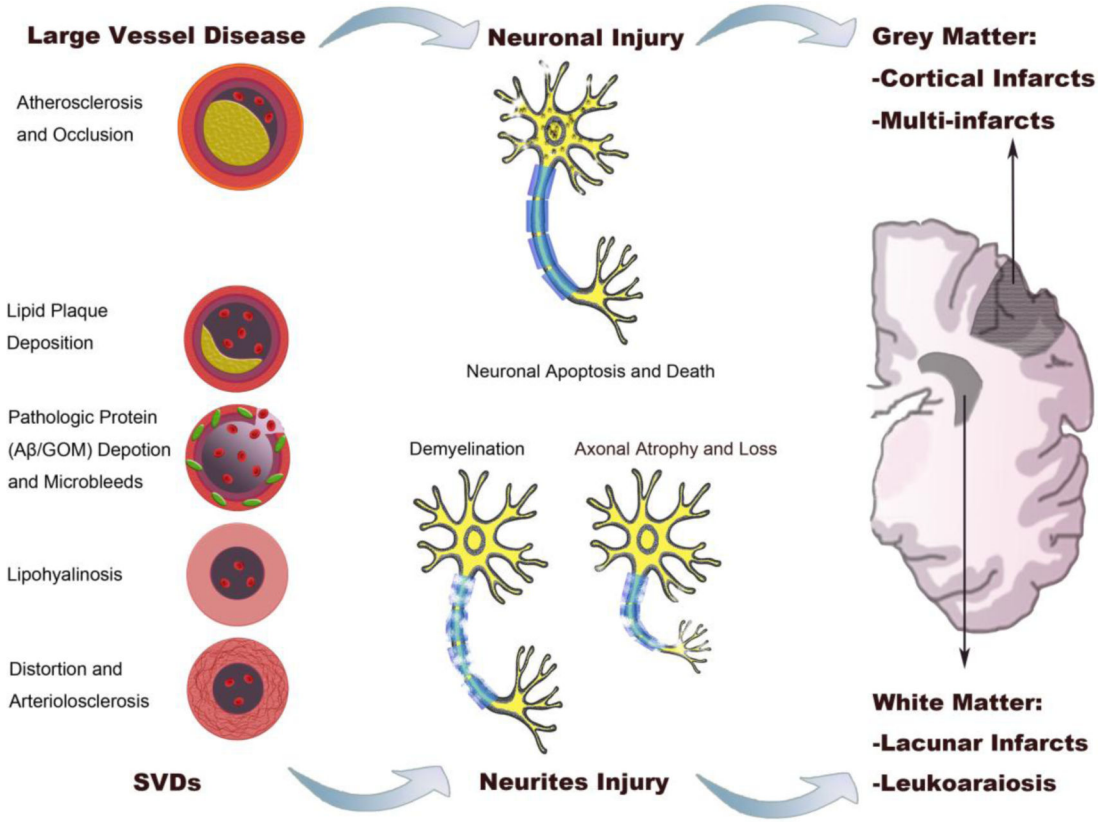

Fig. 2. Vascular and neural pathology underlying VCID

The left panel represents diverse vascular pathologies in VCID. Large vessel diseases, including atherosclerosis and arterial occlusion, cause neuronal death (middle upper panel) or cerebral infarction. SVDs (left lower panel) typically cause neuritic injuries (middle lower panel), such as demyelination and axonal injuries. According to neuroimaging studies, VCID lesions can be observed in both gray and white matters (right panel). Among the lesions, cortical infarcts (typically multi-infarcts) are common in post-stroke VCID, while lacunar infarcts and leukoaraiosis are mainly located at periventricular regions. SVDs: small vessel diseases; Aβ: amyloid-β; GOM: granular osmiophilic material.

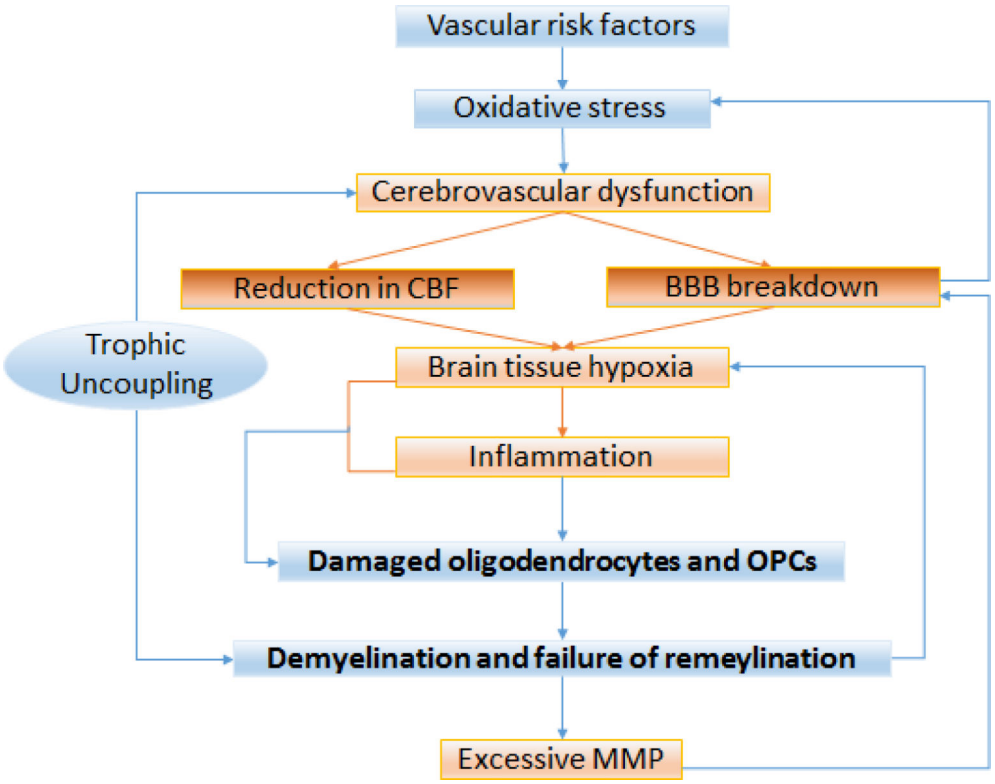

Fig. 3. Pathophysiology of WM injury in VCID

Vascular risk factors such as aging, hypertension, and diabetes result in systemic oxidative stress, which may induce cerebrovascular disorders. Two major consequences of cerebrovascular dysfunction are CBF reduction and BBB breakdown, leading to brain tissue hypoxia and inflammation. WM is particularly vulnerable to hypoxia, leading to damaged oligodendrocytes and OPCs. Loss of trophic coupling facilitates demyelination and interrupts remyelination, thereby predisposing axons to atrophy. Due to increased energy consumption during the action potential, tissue hypoxia is exacerbated. Injured OPCs secrete MMP, which amplifies BBB breakdown, leading to a feed-forward cycle that is vascular-oriented and culminates in WM injury.

Table 1

Animal models for VCID

Type of VCID	Models		References
Ischemic VCID	Cortical Infarcts	2VO/BCCAo	(Lee et al., 2015; Soria et al., 2013; Zhang et al., 2014b)
		4VO	(Kim et al., 2011; Neto et al., 2005; Pulsinelli and Buchan, 1988; Pulsinelli and Brierley, 1979)
		UCCAO	(Yoshizaki et al., 2008; Zhao et al., 2014)
		BCAS	(Nishio et al., 2010; Shibata et al., 2004)
	Subcortical Infarcts	Cerebral emboli	(Purandare et al., 2012; Zhang et al., 2013)
		Cholesterol crystals	(Wang et al., 2012; Zhang et al., 2013)
		Micro-sphere	(Miyake et al., 1993; Takagi and Takeo, 2003)
		Notch3 mutation	(Serlin et al., 2011; Wallays et al., 2011a)
	Risk factors induced VCID	High fat diet	(Miyake et al., 1993; Morrison et al., 2010)
		Hypertension with SHR	(Yamaguchi et al., 1994a; Yamori et al., 1976)
		Diabetes	(Alvarez et al., 2009; Serlin et al., 2011)
		Hypercholesterolemia	(Bell et al., 2012; Nishitsuji et al., 2011; Rodriguez et al., 2013)
		Diet induced-hyperhomosysteinemia	(Fuso et al., 2012; Sudduth et al., 2013; Troen et al., 2008)
Hemorrhagic VCID	ICH	Intraparenchymal bacterial collagenase (Type IV-S)	(MacLellan et al., 2009)
		Intraparenchymal bacterial collagenase (Type VII-S)	(Hartman et al., 2009)
	CAA	Tg2576 mice treated with angiotensin II and L-N^G-nitroarginine methyl ester	(Passos et al., 2016)
		Tg2576 mice treated with dipyridamole-supplemented high-fat diet	(Fisher et al., 2011)
		APP23 mice	(Winkler et al., 2001)