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MOLECULAR PATHOPHYSIOLOGY OF VASCULAR DEMENTIA

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ABSTRACT
Dementia is a term to describe neurodegenerative diseases that affect cognition and memory. It is an umbrella term covering various dementing disorders including vascular dementia, Alzheimer's dementia, Parkinson's dementia, frontotemporal dementia, and Creutzfeldt-Jakob disease. Dementia not only causes impairment of quality of life of the patients but also increases the burden of the caregiver. It is becoming more common despite advances in the biomedical field and a worldwide increase in life expectancy. This is due to a sedentary lifestyle adopted in this modernized era. Alzheimer's disease is the most common form of dementia followed by vascular dementia. Both dementias share the most common risk factors such as aging and vascular risk factors.Vascular dementia is thought to be caused by vascular disorders or impairments. Nevertheless, the exact mechanisms underlying vascular dementia are yet to be determined. Hence, this review intends to provide current findings on the molecular mechanisms of vascular dementia, which maybe helpful in a more thorough understanding of vascular dementia and hence bring some insights into the design of both pre-clinical as well as clinical studies of vascular dementia.
Keywords: White matter damage, Neuroinflammation, Oxidative stress, Hypoxia, Mitochondrial dysfunction.

INTRODUCTION
Vascular dementia (VaD) describes the worsening of cognition and memory secondary to cerebrovascular diseases that decrease blood flow to the brain. It is the second most frequent cause of cognition deterioration after Alzheimer's disease (AD) [1]. Further, VaD involves two main elements which are dementia and cerebrovascular disorder [2].The three common types of sporadic VaD are multi-infarct dementia, strategic infarct dementia, and subcortical vascular encephalopathy while the most seen familial VaD is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [3]. Around 48 million people are suffering from dementia throughout the world in 2015. It is estimated that by the year 2030 and 2050, the number of cases would upsurge to 76 million and 132 million respectively [4]. Patients with VaD may show the following symptoms: forgetfulness, impaired perception, declined executive function, disorientation, depression, and anxiety, and declined ability to solve the problem [5]. Moreover, VaD is associated with an immense burden not only to healthcare institutions but also to the caregivers [6].
VaD is heterogenous where the lesions formed involve different brain areas that are critical for cognitive function. These lesions disrupt the basal ganglia cortical, cortico-cortical, and ascending pathways [7]. Besides, the afferent connections between frontal and limbic cortical structures are disrupted as well. The cortical and hippocampal changes, as well as the subcortical interaction, determine the form of cognitive impairment. The severity of cognitive impairment is associated with the extent of frontal lobe atrophy [8]. Cognition decline is attributable to cholinergic dysfunction and this happens due to the presence of abundant cholinergic tracts in the insulted area of the brain [9]. However, most of the patients with VaD have microangiopathy-related cerebral damage but do not show clinical symptoms or present with vague neurological findings [10].

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One of the common findings among VaD patients is cerebrovascular dysfunction with diminished vascular integrity. It happens due to continuous vascular remodelling as a result of vasculature damage. Abnormal hemodynamic changes cause neurovascular and brain injury by disrupting prefrontal cortical-basal ganglia networks, WM, and the hippocampus [11]. Consequently, a wide range of pathological outcomes ensues such as reduced CBF, thromboembolism, hypoperfusion, oxidative stress, and neuroinflammation. Hence, the neurovascular integrity is very essential because it can provoke and aggravated by hypoxia, neuroinflammation, oxidative and nitrosative stress as well as blood-brain barrier (BBB)

disruption. All these aspects will worsen the progression of patients along the continuum [3].

The neurovascular unit (NVU), as shown in **Figure 1**, comprises neurons, vessels, astrocytes, microglia, and pericytes which serve to regulate cerebrovascular functions. Cerebrovascular dysfunction, inflammation, and oxidative stress damage the NVU leading to aggravated insult to the brain [12]. The effects of NVU dysfunction can be extended to WM damage due to vasoconstriction and platelet adhesion within endothelium leading to vascular occlusion and reduced CBF [5].

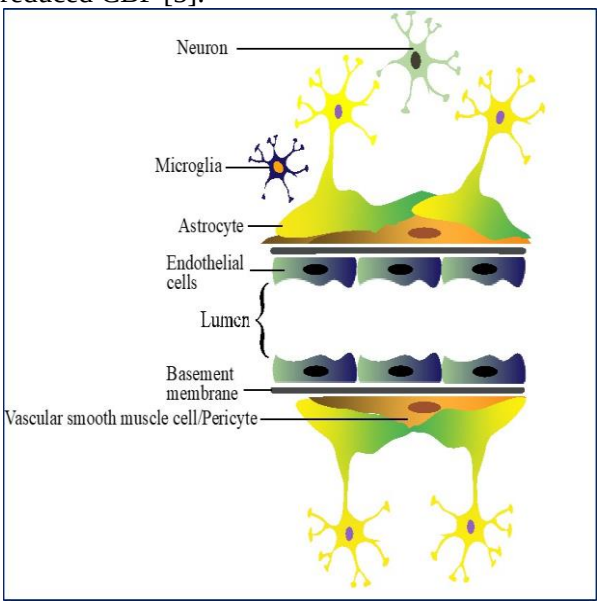

Figure 1: Composition of NVU

Typically, VaD is linked with small vessel disease (SVD), atherosclerosis (AS), and cerebral amyloid angiopathy (CAA), particularly in older people. SVD involves arteriosclerosis, arteriolosclerosis, and lipohyalinosis of small vessels. It may cause microinfarct, lacunar infarct, microbleed, and haemorrhage [13]. AS is a progressive disease of vessels and it involves thickening of tunica intima and deposition of cholesterol in the wall of arteries. Overtime, this may result in the formation of atherosclerotic plaques which reducethe lumen of vessels and reduce the blood flow. The plaques may cause thrombosis at the affected site or embolism upon traveling [14].

On the other hand, CAA is a disease where amyloid-beta proteins (Aβ) accumulate within cerebral vessel walls. This can lead to occlusion of cerebral vessels, impeding cerebral blood flow resulting in microinfarcts or microbleed and hemorrhage. CAA usually happens in neocortical and leptomeningeal vasculature [8]. Large artery disease (LAD), typically due to atherosclerosis or cardioembolism is the core reason cortical and subcortical infarcts related to major arteries supplying the brain while SVD is commonly caused by arteriolosclerosis [15]. SVD is responsible for white matter (WM), thalamus, and basal ganglia lacunes. Pure VaD cases are associated with more severe deep gray and WM lacunar infarcts compared to those with stroke and old, non-demented people [16]. When compared to AD, the prefrontal neuronal circuits, and thus the executive functions are more affected in VaD. Hippocampus and memory are more affected in AD [10].

MORPHOLOGICAL SUBSTRATES OF VAD

VaD can be classified into three major forms depending on the form of occurrence of brain lesions, namely multi-infarct dementia, strategic infarct dementia, and subcortical vascular encephalopathy.In multi-infarct dementia, brain lesions occur in different brain regions [2]. These can be due to hemodynamic changes, hardening of main arteries supplying the brain like the carotid artery, microinfarcts owing to embolism, WM damage, subcortical lacunes, and hypoperfusion of the brain [17]. The examples of multi-infarct dementia include subcortical arteriosclerotic leukoencephalopathy (SAE), pseudolaminar cortical necrosis, hippocampal sclerosis as well as post-ischemic lesions [8]. In strategic infarct dementia, lesions occur in brain regions which are crucial functionally. For example, hippocampus, frontal lobe, and thalamus [6]. The focal lesions may be the result of large and small vessel disease, hemodynamic changes, embolism, hypoxic ischemia, and angiopathies. On the other hand, subcortical vascular encephalopathy is symbolized with WM lesion [13].

The pathological changes that occur in VaD are vast due to different cerebrovascular lesions. These lesions cause impairment of cognition and include large; infacts in cerebral arteries like medial cerebral artery and posterior cerebral artery, lacunar infarcts, microinfarcts, WM lesions, hippocampal sclerosis and pseudolaminar cortical necrosis [18]. These lesions can be classified according to large and small vessel disease. Infarcts involving major arteries supplying the brain are evident in large vessel dementia. AS of these arteries are enhances the thromboembolism and subsequently hypoperfusion. Cerebral arteries AS is associated with more serious lesions in the circle of Willis among patients with VaD compared to normal controls. Apart from the major cerebral arteries, lesions can also be

observed in leptomeningeal arteries and perforating arteries [8].

Lacunes, microinfarcts, and microbleed are usually observed in SVD. They are commonly found in WM and subcortical structures such as basal ganglia, thalamus, brain stem, and cerebellar WM. These lesions result from microvascular changes and hypoperfusion [19]. Lacunar infarcts are the most common neuropathological substrate of VaD [8,16]. They occur due to restricted lumen of penetrating vessels causing ischemic necrotic sites.Lacunes may appear as minor hemorrhage, reabsorbed hemorrhage, or dilated perivascular spaces. Cerebral microinfarcts, neuronal loss, gliosis, and cystic lesions can be commonly found in VaD cases in all brain regions [20]. The presence of microvascular infarcts is associated with poor prognosis in older people.

Manifold cortical microinfarcts impair semantic memory, speed of processing information, and increase the likelihood of dementia [16]. Multiple lacunar infarcts are associated with poor cognition and a greater risk of dementia [21]. In strategic infarct, the lesions are situated in particular brain areas like thalamus and basal ganglia. In SAE, infarctions mainly occur in WM. Border zone infarcts occur in cerebral convexities as a result of hypoperfusion [22].

MOLECULAR PATHOPHYSIOLOGY

The progression of VaD is a heterogeneous process; its underlying pathophysiology is diverse. In this section, detailed molecular mechanisms of VaD pathophysiology will be discussed. **Figure 2** outlines the overview of VaD pathophysiology.

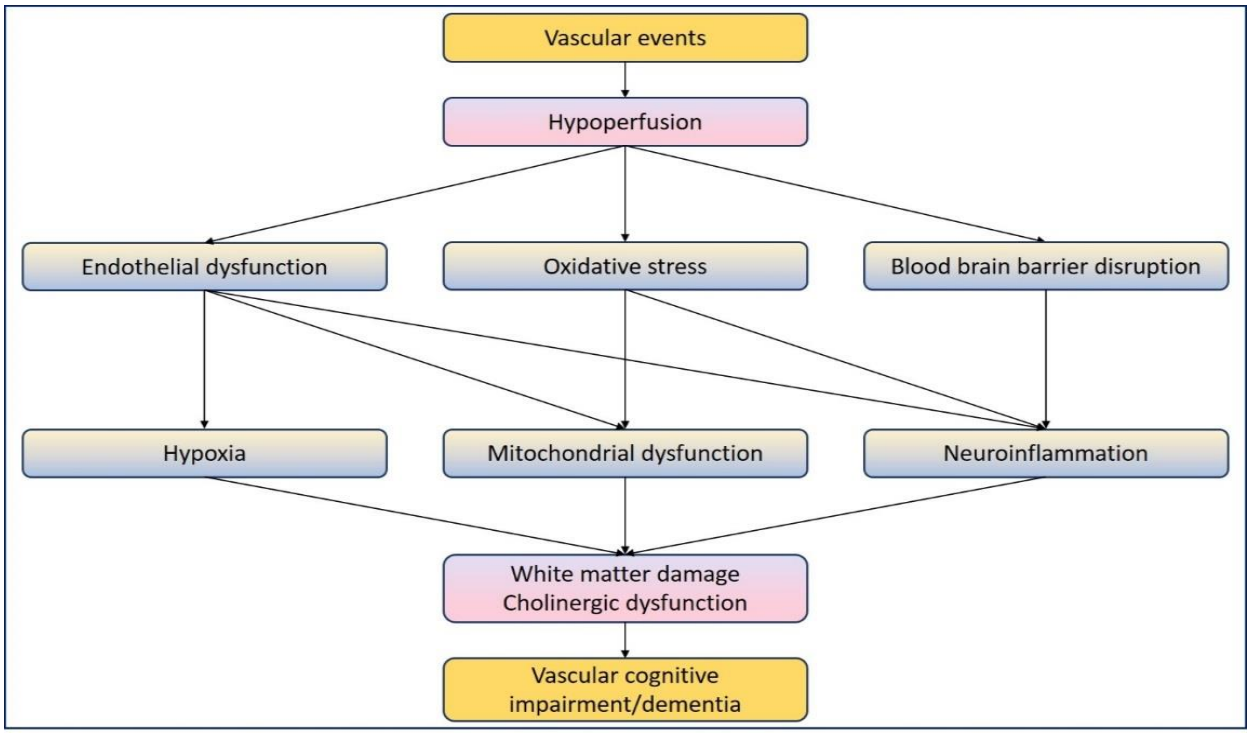

Figure 2: Overview of VaD pathophysiology

White matter damage

WM lesions involve WM rarefaction, lacunes, gliosis, dilatation of perivascular space, demyelination, and axonal damage. WM damage happens mostly due to SVD [16, 21]. Cerebral WM is prone to damage due to hypoperfusion limited collateral blood flow. The systemic level of asymmetric dimethylarginine (ADMA), a NO synthase inhibitor, is increased with WM lesions. ADMA reduces arterial vasodilation in response to NO. The occurrence of WM lesions results in diminished brain glucose consumption and CBF, interruption of brain connectivity, and brain atrophy [6]. WM damage is attributable not only to hypoxia but also inflammation. Reactive gliosis occurs following neuronal damage and is associated with increased expression and pro-inflammatory cytokines that activate the pro-inflammatory nuclear factor kappa B (NF-kB) pathway [23].

Besides, demyelination of axon, disintegration, and disruption of the integrity of WM also occur. Consequently, oligodendrocytes are subjected to hypoxic injury and they shrink and die, which halts demyelination of neurons [3]. Oligodendrocytes are important for the axonal survivability. Demyelination causes the axons to

be more vulnerable to free radicals and hypoxic damage. The energy production by axon is hampered due to the malfunctioning of sodium-potassium (Na^+/K^+)ATPase [24]. This results in the built-up of Na^+ ions within cells and sodium-calcium (Na^+/Ca^{2+}) exchanger function reversal, followed by Ca^{2+}ions accumulation within cells. Fragmentation of microtubules and disruption of axonal flow then occurs via Ca^{2+} activated protease. The upregulation of voltage-dependent Na^+ channels further exacerbates this condition [6]. Oligodendrocytes damage can be reflected by the reduction of myelin-associated glycoprotein (MAG) to proteolipid protein 1 (MAG:PLP 1) ratio in both WM and cerebral cortex [16]. Eventually, the neuronal transmission is impeded and leads to cognitive impairment [3, 5]. Other than oligodendrocytes, oligodendrocyte progenitor cells (OPC) are also affected. They are prone to hypoxic insult and damage induced by extracellular adenosine triphosphate (ATP). Hyaluronan (HA) is an important substance for neuronal migration. In regions of WM damage, HA is degraded by hyaluronidase PH 20. Hence, the maturation of OPC into oligodendrocytes and thus remyelination is halted [6].

WM lesions, independent of their site, negatively affect the function of the frontal lobe. These lesions are more commonly found in neocortical structures and are associated with a higher risk of dementia in cases of SVD with lacunes [12]. Lesions those are located in the thalamo-cortical, striato-cortical, and prefrontal-basal ganglia pathwaysimpair cognitive function, memory, and behavior. Besides, it has been found that impairment of cognition is linked lacunar infarct present in gray and WM, which disrupts the subcortical-frontal circuit [8]. WM insult can also be manifested as spongiosis, a process that involves WM vacuolization and dilatation of perivascular spaces. The boundaries of areas where spongiosis happens cannot be clearly defined. These alterations can be related to persistent pro-thrombotic endothelial disruption due to SVD [16].

Cholinergic system

The cholinergic system is crucial for cognition, including execution, memory, and emotion control. Deficient of this system is associated with a significant decline in executive function. Cholinergic dysfunction most commonly occurs in the basal forebrain cholinergic nuclei and reduce cholinergic connections to the cortex [4]. Cholinergic dysfunction may also due to the reduction of affinity of receptors towards ligand. It was reported that CBF and cholinergic signalling affect each other reciprocally [25].The widespread WM and vascular lesions result in disruption of cholinergic connections, ultimately leads to dysfunction of the cholinergic system. This contributes to the decrease in cerebral blood flow (CBF) and subsequently brain hypoperfusion [8]. Impairment of the cholinergic system was evident in both animal models and clinical studies of VaD. In animal models of VaD, the loss of cholinergic neurons reduced choline acetyltransferase (ChAT) activity, decrement in m3, and m5 muscarinic acetylcholine (ACh) receptors expression, lowered Ach level and worsen memory and learning. On the other hand, decreased cholinergic neurons, ChAT activity, level of ACh in cerebrospinal fluid (CSF), and Ach activity, as well as the loss of cholinergic nerve supply towards the lesion areas, are observed in VaD patients [9]. Patients with mixed dementia show a more serious reduction inChAT activity with patients with VaD and normal control [8]. ChAT is essential for the synthesis of ACh.

Endothelial dysfunction

Nitric oxide (NO) has a role to play in regulating vascular tone, maintaining neurovascular homeostasis, assisting and neurotransmission, and modulating immune responses. It modulates the tone of vessels, junctional permeability, platelet accumulation, and leukocyte adhesion in endothelial cells [26]. In cases of VaD, the level of NO in cerebrovascular endothelium reduces, compromising the vasodilating activity of endothelium and thus leads to a reduction in CBF. This in turn provokes the built-up of oxygen and nitrogen radicals which increase oxidative and nitrosative stress [27]. These phenomena are associated with inflammation with the involvement of pro-inflammatory cytokines like interferon-gamma, interleukin (IL) 21b, and tumor necrosis factor-alpha (TNFα). Subsequently, BBB disruption follows, resulting in hypoperfusion due to reduced CBF [28]. Apart from that, the reduction of NO level in endothelium increases the expression of amyloid-beta precursor protein (AβPP) and β-site AβPP cleaving enzyme-1 (BACE-1), ultimately lead to more Aβ production [3].

Mitochondrial dysfunction

The brain mitochondrial respiratory chain enzymes are susceptible to hypoxic injury and produce reactive oxygen species (ROS) upon the damage, leading to dysfunction of mitochondrial

pyruvate dehydrogenase. This enzyme is responsible for generating acetyl coenzyme A to produce ATP. As a result, the production of ATP is impaired and leads to the unmet energy demand of neuronal cells [29]. Mitochondrial injury is also found to be associated with amyloid deposits and atherosclerotic lesions, indicating that distinct but interconnected factors may cause mitochondrial dysfunction. Hypoxia hampers the expression of optic atrophy-1 and mitofusin-2 and aggravates brain mitochondrial damage, worsening spatial cognition, and memory [3].

Under physiological conditions, there is a state of equilibrium between biogenesis and mitophagy, where mitofusin-1, mitofusin-2, and optic atrophy-1 are responsible for mitochondrial fusion while dynamin-related protein-1 (DRP1) and fission protein-1 are responsible for mitochondrial fission. Biogenesis is brought by peroxisome proliferator-activated receptor γ coactivator-1a. It recruits transcription factors like nuclear respiratory factor-1 (NRF-1), nuclear respiratory factor-2 (NRF-2) and mitochondrial transcription factor A. NRF-1 and NRF-2 control the transcription of nuclear and mitochondrial genes concerned with electron transport (complex I–V), mtDNA transcription or replication, oxidative phosphorylation, heme biosynthesis, protein import/assembly, ion channels, shuttles, and translation [3, 30]. Mitochondrial dysfunction occurs due to changes in the dynamics of mitochondrial biogenesis and turnover. Neurodegenerative disorders disturb the state of equilibrium, resulting in mitochondrial dysfunction. For example, Aβ triggers S-nitrosylation and hyperactivation of DRP1, disintegratingof mitochondria, compromised biogenesis, and synaptic injury [3].

Neuroinflammation

Ischemic insult to the brain due to hypoxia upregulates various mediators of inflammation like TNF-α, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), NO and IL-1b.These mediators recruit peripheral leukocyte and activate both astrocyte and microglia. Vessels occlusion may also occur due to the recruitment of peripheral leukocytes. Astrocyte and microglia release inflammatory cytokines, NO, ROS, and glutamate which cause further damage and disrupt BBB [9]. Impaired BBB integrity allows extravasation of fibrinogen, complement proteins, and antibodies. The extravasated fibrinogen interacts with integrin and non-integrin receptors, thereby activating pathways of inflammation [6]. The interactions between astrocytes and microglia are mediated by the production of inflammatory signals. Astrocytes possess IL receptors, activation of IL-1b & TNF, they secrete cytokines for microglia for positive or negative feedback cycle. On the other hand, microglia become phagocytotic and produce IL-1b and TNFunder hypoxic conditions [31]. Microglia is also release IL-17, IL-6, and chemokine ligands (CXCL) which lead to neuroinflammation after ischemia. Both astrocytes and microglia differentiate into distinct phenotypes according to the activation signals but the precise mechanisms are yet to be explored [25].

The macromolecular complex called inflammasome plays a crucial role in neuroinflammation. It consists of receptors for pathogen-associated molecular patterns (PAMP), procaspase-1 along with an adaptor. The adaptor is an apoptotic speck-containing protein with a caspase recruitment domain (ASC), responsible for caspase-1 maturation. ASC is recruit following oligomerization of procaspase-1, where the ASC serves as an enucleating template and binds other inflammasomal components [32]. This in turn leads to the production of fibril or prior-like structures. In the presence of PAMP, inflammasomes stimulate caspase-1 and caspase-8 activation, resulting in pyroptosis and apoptosis of neuronal cells respectively. The caspase-1 will also cleave proIL-1b and proIL-18 into their mature form as well as secrete inflammatory cytokines [3]. IL-1b brings about an increase in macrophages, astrocytes, and microglia, which accumulate in the neurovascular injury site, secrete more inflammatory mediators (IL-1b, IL-6, TNFα, free radicals and NO) and cause further neuronal damage [10]. The survivability of neurons is reduced due to weakening integrin-linked kinase signalling, resulting in lower brain-derived neurotrophic factor (BDNF). Besides, the ectodomain of tropomyosin receptor kinase B (TrkB), the receptor for BDNF, on neuronsis cleaved by endothelial matrix metalloproteinases (MMP) 9. This ensures decreased neurotrophic signalling and neural plasticity [6]. TrKB receptor, Ras mitogen-activated protein kinase (Ras-MAPK), phosphoinositide 3-kinase (PI3K) and phospholipase Cγ (PLC) facilitate BDNF cell signalling. They stimulate proliferation, differentiation, the survival of neurons, and activity at the synapses. These actions help in long-term potentiation (LTP) which is important to maintain neuronal plasticity [33]. Hippocampal inflammation hinders the proliferation of neuronal progenitor cells, synthesis of neurons as well as

synaptic plasticity, resulting in memory and learning impairment [5].

Oxidative stress

The production of surplus oxygen and nitrogen reactive species result in alteration of redox status and lead to impairment of mitochondrial electron transport chain (ETC), oxidative damage on protein molecules, and damage of DNA [34]. Due to the high composition of polyunsaturated fatty acids in the brain, this organ is particularly vulnerable to high oxidative or nitrosative stress. Under high oxidative/nitrosative stress, aldehydes that are toxic to brain cells are formed and promote brain damage due to oxidation. On top of that, vascular and cellular caspases, endonucleases, and translocases are stimulated, contributing to apoptosis [3]. Nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) also plays an important role in this context. It produces superoxides under inflammatory and hypoxic conditions [35]. The generated superoxides not only inactivate NO but also generate other ROS and reactive nitrogen species such as hydroxyl radicals ($OH\cdot^{-}$), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO\cdot^{-}$) [25]. These reactions cause endothelial, neuronal, and glial cells insult. Further, the uncoupling of NVU and the reduction of CBF follows [5].

Hypoxia

Hypoxic insults to the brain can lead to neuroinflammation, BBB disruption, and vascular dysfunction. The responses of cells towards hypoxia are brought by the activation of the hypoxia-induced factor-1 (HIF-1) pathway. HIF-1 participates in cellular stress and inflammatory response following hypoxic insult as well as modulates the expression of pro-survival genes such as vascular endothelial growth factor (VEGF), glucose transporter-1, and erythropoietin [36]. HIF-1 has two subunits establishing a transcriptional dimer, namely HIF-1a and HIF-1b. The activity of HIF is reliant on the availability of the former. In physiological conditions, proline hydroxylases (PHD) regulate the activity of HIF-1a by degrading it via hydroxylation. HIF-1 accumulates and stabilizes under hypoxic conditions due to the inactivation of PHD. Upon translocation of HIF-1 from the cytosol into the nucleus, it increases the expression of prosurvival genes [3, 37].

To add on, nitric oxide synthase (NOS) is stimulated under hypoxic condition contributes to excessive production of NO. This increases the production of free radicals that damage mitochondria and NVU [5]. The mitochondrial ETC is disrupted by hypoxia, causing an increase in the generation of ROS. This in turn changes the redox state, leading to a higher level of Fe^{3+} ions as compared to that of Fe^{2+} ions and thus diminishing of PHD activity [3].The cerebrovascular endothelial cell and BBB are disrupted and more inflammatory markers such as matrix metalloproteinases (MMPs), IL, TNFα, toll-like receptor 4 (TLR4); C-reactive proteincan penetrate BBB; resulting in microglia & astrocytes stimulation; worsen vascular dysfunction;edema; and neuropathology [5, 6].

Genetics

Genetic diseases may also cause VaD. The most common familial SVD is CADASIL [3, 21]. It happens due to mutations of the Notch 3 gene [5, 16]. Most of the time, missense mutations occur in exon 3 and alter the number of cysteine residues.This gene encodes the Notch 3 receptor which regulates the proliferation and differentiation of smooth muscle cells. Notch 3 gene is commonly expressed in the vascular smooth muscle cells (VSMC) as well as pericytes [10]. The pathological hallmark of CADASIL is the deposition of granular osmiophilic material (GOM) in both vascular and perivascular cells [6].In CADASIL, the brain VSMC undergoes apoptosis and there is a thickening of the vessel wall as well. Consequently, the vessels lose their ability to dilate in response to fluctuation in blood pressure. This results in reduced CBF and infarction of both gray and white matter. In the WM, demyelination, damage of axons, neurons apoptosis, astrocytopathy, cortical atrophy, and declined frontal cognition occur [16]. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a rarer familial SVD. It happens due to mutations of transforming growth factor-beta (TGF-β) repressor HTRA1 gene [6, 21]. In CARASIL, arterial medial smooth muscle cells are lost with serious leukoencephalopathy plus lacunar infarcts [16]. Another gene that contributes to the development of VaD is apolipoprotein E (apoE). It has been suggested that the apoE4 allele, which increases the likelihood of brain hemorrhage is a risk factor for both VaD and AD. ApoE is reported to be present in the hippocampus of VaD [5, 6]. ApoE4 can also cause BBB to lose its integrity via activation of an inflammatory pathway that entails cyclophilin A. Upon activation, MMP 9 is released and damage the basement membrane protein and tight junctions of endothelia [6].

Small vessel disease (SVD)

SVD was claimed as the typical cause of VaD and a major contributor to the occurrence of infarcts. Patients with SVD often present with WM lesion and lacunar infarcts in both gray and WM, which are correlated with cognitive decline and dementia [21]. The pathological findings associated with SVD can be found in as well as a facet of cerebral microvessels from arteries to venules.These findings include hyalinosis, fibrinoid necrosis, astrocytic gliosis, dilatation of perivascular space, and myelin pallor. Both gray and WM injuries are observed in SVD [6, 16]. SVD may cause intracranial hemorrhage (ICH) in the form of microbleed, lobar hemorrhage, or subarachnoid hemorrhage. While macroscopic hemorrhage is infrequently seen, microbleed or microscopic haemorrhage occurs more often and in severe CAA [38]. Apart from that, SVD can also white matter hyperintensities (WMH). The severity of SVD is correlated with the extent of cognitive impairment where lacunar infarct, WM lesions, and periventricular demyelination worsen cognition [8].

SVD may also alter the small cerebral vessels results in hypoperfusion which in turn causes lacunar and microinfarcts. Subcortical lacunar infarct and widespread microinfarcts are the most prominent characteristic of VaD [39]. Arteriolosclerosis impairs the ability of vessels to dilate or constrict in maintaining blood pressure homeostasis. This leads to hampered responses towards blood flow variation and thus affect brain perfusion. Besides, the generation of NO is reduced while its degradation is upregulated in SVD, ensuing endothelial dysfunction [40]. Furthermore, the BBB is also likely to be disrupted which causes the accumulation of fluid and macromolecules within the WM.The increased permeability of BBB allows more lymphocytes and macrophages to bypass it and exacerbates inflammation [16]. Microinfarcts negatively impact both episodic and semantic memory along with information processing speed and therefore, escalating the risk of dementia. It was found that brain lesions due to SVD are correlated with diminished network efficiency. The lower the network efficiency, the higher the risk of dementia because it regulates the executive function and loss of gray matter in the frontal lobe [21].

Cerebrovascular dysfunction

Both large and small vessel alterations contribute to the development of VaD. The reduction of CBF was observed in cases with arterial stenosis but without infarct [6, 10]. Insufficient blood supply to the brain causes neuronal death, brain atrophy, and neurovascular uncoupling [25]. Hemodynamic failure due to occlusion of the carotid artery is correlated with cognitive decline [21]. The alterations of small vessels are correlated with lacunes, WM damage, loss of BBB integrity, and accumulation of fluid and macromolecules in WM [10]. The initial and usual pathological change of VaD is the alterations of the vascular wall, probably due to arteriolosclerosis or CAA. Then, dilatation of perivascular space and occurrence of microinfarcts follow. The former is probably due to hypertension, inflammation, brain atrophy, and alteration of perivascular flow [21]. These changes are first seen in the frontal lobe, then in the temporal lobe followed by basal ganglia. It was reported that patients who lost their lives due to cerebrovascular disease generally had impaired frontal executive function, attention, and information processing speed [41]. The focus has been put on the arteries and arterioles while narrowing and occlusion of venous lumens may also occur due to the deposition of collagen in the vessel walls. The extent of collagenosis is even more in brains with WM damage. The hardening of vasculatures due to deposition of collagen may cause ischemic insult or edema in WM [16].

Disruption of BBB occurs commonly in VaD, demonstratable by increasing the level of albumin in the cerebrospinal fluid (CSF) and the appearance of fibrinogen and antibodies in WM. The Aβ in the brain is removed via drainage into perivascular spaces and transport across the BBB mediated by the low-density lipoprotein receptor-related protein-1s (LRP-1) [42]. Dilatation of perivascular space and insufficiency of LRP-1 result in reduced Aβ elimination. The latter is caused by an increased serum response factor and myocardin [6]. So, the CSF level of Aβ increases in BBB disruption, favoring the development of amyloid plaques in the brain vessels. This in turn deteriorates endothelial function. The Aβ-42 contributes towards the accumulation of amyloid plaques and correlated with cerebral atrophy and impaired cognition. On the other hand, Aβ-40 may cause microbleed which is associated with reduction of global cognition, visuospatial, and executive functions [25].

The NVU is the cornerstone of the regulation of CBF. Endotheliallayer damage leads to a reduction of NO release. Subsequently, VSMC lostits vasodilating activities followed by the reduction of CBF. Direct injury to VSMC can also affect

neurovascular coupling. On the other hand, pericytes become hyper-contractile under the ischemic condition which causes reduced blood flow to the brain and WM damage. Astrocytes and glial cells regulate vascular tone by working together with VSMC and pericytes [43]. The activation of phospholipase A2 pathway results in vasodilation while the activation of phospholipase D2 pathway results in vasoconstriction. Astrocytes and glial cells damage impair the NVU function but the precise mechanisms remain unclear [25]. To add on, subjects with vascular risk factors have declined functionality of endothelial progenitor cells (EPC), where the colony-forming units' capability in forming vasculature is diminished. This is associated with a decreased level of angiogenic T cells which is important for endothelialcell repair by EPC [6].

Intracerebral micro-hemorrhages

Cerebral microbleed refers to extravasation of blood into the perivascular space with the adjacent tissues remain intact. Microhaemorrhage that occurs in the cortical region is mostly due to CAA while that in deep brain areas is due to WM damage caused by vascular pathologies [44]. Extravasation of haemosiderin has been observed in intracerebral micro- hemorrhage or microbleed. Apart from hypertension, CAA and neurodegeneration may contribute towards cerebral microbleed [45]. There is a correlation between the number of microbleed and cognition. An increasing number of microbleed is associated with slower psychomotor speed and poorer execution ability [16]. The structural connectivity and neuronal network function are disturbed by micro-hemorrhage [21].

Cerebral amyloid angiopathy

CAA refers to a disease where Aβ deposits in the cerebrovascular wall, mostly affecting the arteries and arterioles. The deposition of Aβ in tunica media and tunica adventitia results in smooth muscle cells and pericytes degradation. CAA is the main reason fora brain hemorrhage, resulting in cerebral ischemia [6]. It is frequently associated with cerebrovascular diseases and serves a neuropathological feature of cognitive impairment. The occurrence of cerebrovascular lesions is correlated to the severity of CAA. Hereditary CAA due to a genetic mutation is featured with an extensive accumulation of Aβ within vessel walls as well as hemorrhagic and ischemic infarcts. Severe CAA on its own can make dementia happen [16]. CAA is related to the formation of the neurofibrillary tangles, neuritic plaques deposition, and apolipoprotein E ε4 allele. The global cognition, information processing speed along with episodic and semantic memory of patients with CAA deteriorates at a higher rate compared to those without CAA. The underlying mechanisms include WM ischemia, microbleed and hemorrhage, microinfarcts, and disturbed integrity of neuronal network [21].

Brain atrophy

Degradation of neurons can occur following subcortical ischemia. This is governed by the deterioration of neurons linking the site of vascular ischemia with gray matter, causing WM loss and cortical rarefying. The exact mechanism remains unclear but may entail inflammation, transsynaptic effects, and retrograde degradation of cortical neurons to the subcortical level. The consequences of subcortical ischemic lesions on cognition are governed by the loss of gray matter in the cortex. The brain atrophy is one of the best prognostic parameters of cognition loss in cases of pure VaD [21].

CONCLUSION

Cerebrovascular diseases cause impairment of functional hyperemia. Particularly, endothelial dysfunction and BBB disruption occur. These result in a reduction in CBF which ensues hypoxia in brain tissues. Under the condition of insufficient oxygen and energy, the oxidative stress within the brain increases. This provokes inflammatory reactions and causes further damage to the brain and cerebral vasculature. Astrogliosis and oligodendrocytes insult follow which leads to demyelination, axonal disintegration, and neuronal death. Consequently, WM damage and disruption of neuronal networks happen and ultimately lead to cognition impairment. Despite the current understanding of the molecular pathology of VaD, there is still a lot of aspects remain unclear. The progression of VaD is a heterogeneous process and shares common risk factors with other diseases especially AD. It is also challenging to estimate and determine the extent of contribution of each pathological factor towards to progression of VaD as well as the manifestation of associated symptoms. Therefore, more information on the pathological mechanisms of VaD by future research work will shed light on the diagnosis as well as the management or prevention of VaD.

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