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Inflammation, apoptosis and autophagy as critical players in vascular dementia

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Abstract. – Vascular dementia is the second-most cause of dementia, characterized by cerebral infarcts, white matter lesions, myelin loss and often amyloid angiopathy. Hence, vascular damage is a critical cause of neuronal loss and synaptic disintegration. Abnormal neuroinflammation, autophagy and apoptosis are the prerequisite factors for endothelial and neuronal cell damage. This leads to the onset and progression of cerebrovascular disorders and cognitive dysfunction. The innate immune cells, pattern recognition receptors, Toll-like receptor-4 and related inflammatory mechanisms disrupt cerebrovascular integrity *via* glial activation and increased pro-inflammatory interleukins and TNFα. Inflammasome polymorphisms and multi-faceted neuro-immune interactions further integrate systemic and central inflammatory pathways, which induce vascular tissue injury and neurodegeneration. Specifically, chronic cerebral hypoperfusion disrupts the self-cannibalization mechanism of autophagy *via* altered expression of autophagy-specific proteins, Beclin-1, LC3 and P62. The deregulated autophagy pathway causes neuronal loss, hippocampal shrinkage, and ultimate loss in synaptic plasticity. The vascular dementia models typically exhibit downregulated anti-apoptotic Bcl-2 and upregulated pro-apoptotic Bax, cleaved caspase-3, and cleaved-PARP levels in the brain, for which modulated p38 MAPK and JNK phosphorylation pathways play a vital role. Endoplasmic stress-induced apoptosis, calcium overload and glutamate excitotoxicity in combination with ASK1-MAPK signaling mechanism also contribute to the cerebrovascular pathology. Vascular injury reduces neurological scores and increases the infarct volume, DNA damage and neuronal apoptosis in ischemia/reperfusion injury. Additionally, synergistic and additive interactions between inflammasome, autophagy and apoptotic signaling pathways augment symptoms of vascular neurodegeneration. Overall, the current review enlightens the key risk factors and underlying mechanism triggering vascular dementia. The review additionally informs the challenges associated while treating vascular dysfunction, and highlights the need for targeted drugs for reducing cerebrovascular damage.

Key Words:
Cerebrovascular, Cognitive dysfunction, Mechanisms, Inflammasome, Autophagosome, Caspases.

Introduction

Vascular dementia is a pathologic condition of the elderly, characterized by disrupted cerebral blood flow. It is manifested by loss in rationality, judgemental skills and particularly cognitive and memory performances[1]. The vital risk factors for arterial blockade, a key feature of vascular dementia, include heart attack, stroke, atherosclerosis, hypertension, hypercholesterolemia, Type 2 diabetes, insulin resistance, obesity, smoking, and cardiac problems[2]. These cerebrovascular disorders deregulate the cerebral blood vessels, induce functional injury to capillaries, arterioles and venules and damage myelinated axons. Myelin and axon damage further induce white matter lesions and trigger the pathophysiological process of vascular dementia[3]. Cerebral microangiopathy and blood-brain barrier (BBB) disintegration are key features of vascular dementia, essentially caused by vascular wall thickening, collagen accumulation along blood vessels and capillaries, smooth muscle cell atrophy, and lumen thinning.

Currently, as per the World Health Organization (WHO) report based on epidemiological data, around 55-60 million of the world are suffering from vascular dementia, with a projected estimate of 85-90 million by 2030 and 150-160 million by 2050[4]. Incidences of vascular dementia are progressively on the rise, incurring a signifi-

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cant financial expenditure for its treatment, mainly in developed countries and elderly persons. Notably, vascular dementia is the second-most prevalent form of dementia after Alzheimer's Disease (AD), in which patients usually survive for only five-seven years after onset[5]. Due to reduced cerebral amyloid beta (Ab) clearance during cerebrovascular damage and cerebral hypoperfusion, AD and vascular disorders share several overlapping features.

Arterial occlusion and lesions in cortex, basal ganglia and pons, lacunar infarctions in white matter, disrupted endothelial tight junctions and BBB breakdown appear as key morbid characteristics impairing the normal cerebroarterial blood flow for an extended period[6]. Moreover, reasons for vasoconstriction also include vascular wall matrix thickening, undesired collagen accumulation, smooth muscle collapse and lumen contraction[7]. Collectively, cerebral microvessels, particularly capillaries, encompass a large cross-sectional area and play an important role in normal nutrient transportation, hemodynamics and microcirculation in the cerebral cortex[8]. Dysfunction and degeneration of the neurovascular unit, comprising a network of pericytes, myocytes, astrocytes, neurons, oligodendrocytes, endothelial cells and cerebral microsvessels disrupt BBB and accentuate the pathogenesis of vascular dementia[9]. Microvascular damage also hinders nutrient exchange and homeostatic mechanisms that control blood flow and microcirculation along the smooth cerebrocortical blood vessel[10]. Additionally, a synergistic and pathogenic interaction between endothelial and neuronal cells has emerged as a conspicuous reason for cerebrovascular impairment and onset of vascular dementia[11].

Several mechanisms participate in neuronal degeneration and axonal and white matter injury in vascular dementia. Of these, apoptosis and inflammation are the two major pathogenic factors, and currently deregulated autophagic pathways have also been actively considered in promoting vascular pathology[12]. An alteration in these mechanisms triggers aberrant downstream signaling pathways, neurovascular dysfunction, ischemic infarction-induced brain injury, vascular cognitive impairment and an ultimate dementia[13]. These factors inhibit cerebral repair, neuronal cell growth, neurogenesis, synaptogenesis and secretion of trophic and growth factors. Moreover, these pathways alter axon and synaptic plasticity, culminating into cerebral dyshomeostasis, neurodegeneration and brain hemorrhage[10]. Truly, these factors disrupt the complex intercellular interactions between the functional cell types of the brain and their network (Figure 1) that sustain the CNS integrity. Although apoptosis, inflammation and autophagy pathways usually exhibit distinct mechanisms of their own, they often share vascular dysfunction-induced common molecular and regulatory pathways of neuronal survival and death. A cross-talk between these signaling path-

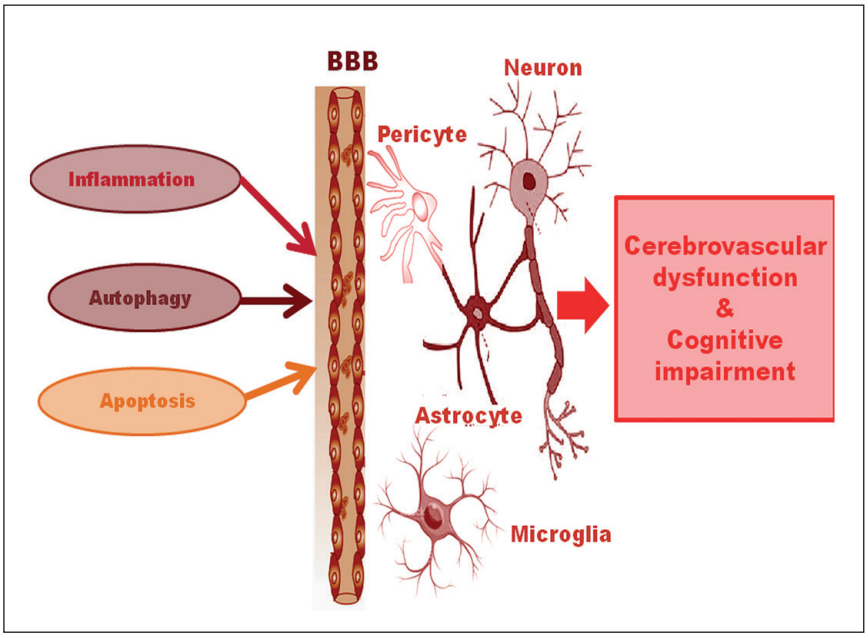

Figure 1. Factors affecting the brain cells and BBB in vascular dementia. Inflammation, autophagy and apoptosis act on the complex cellular network of the brain, guarded by the BBB, triggering cerebrovascular damage and cognitive impairment.

ways participates in cerebrovascular pathologies and myelinated axonal injury, with a concomitant interaction of aging and related risk factors. The pathological features induce a chain of deleterious events and white matter damage, associated with changes in the neuron, glia and myelin health. These pathological features ultimately cause cognitive damage and cerebral atrophy[14,15].

Although several reports elucidate the pathologic mechanisms of vascular dementia, an overall compilation of the signaling pathways in vascular neuropathologies and cerebrovascular dysfunction is unknown. The current review article informs the individual and overlapping risk factors and signaling pathways triggered by inflammation, apoptosis and autophagy mechanisms for cerebrovascular dysfunction and vascular-associated cognitive impairments.

Inflammation and Vascular Dementia

Vascular alterations affect the innate immunity and subsequently activate white blood cells and antigen-presenting cells. This essentially involves the recognition of pathogens and related components released from injured tissues *via* pattern recognition receptors (PRRs). As an immune response, the damaged vascular tissues generate ATP and increase serum levels of inflammatory cytokines, positive acute phase proteins and the high mobility group box protein 1 that functions as a non-nuclear histone protein[16,17]. This also accompanies the release of cell cytoplasmic proteins, as well as a shift of cytoplasmic mitochondrial DNA into the nuclear genome. Inflammation in response to vascular injury involves the stimulation of hypothalamus, pituitary gland, adrenal gland axis and the sympathetic and parasympathetic nervous systems, which move to their normal states following tissue repair. Conversely, a sustained inflammatory situation aggravates tissue damage and alters the systemic inflammation process. These immune responses have a link with the metabolic changes in diabetes mellitus, diabetes insipidus, hypercholesterolemia, arteriosclerotic vascular disease, hypertension, overweight and communicable diseases that are risk factors for cerebrovascular and neurodegenerative diseases. Notably, Magnetic Resonance Imaging (MRI) data reveal glial activation as a part of the inflammation-linked pathological cerebrovascular events[18].

Cerebral sub-cortical small vessel diseases are characterized by vascular white matter lesions, hemorrhage, and cerebral infarcts. The small vessel diseases generally relate with inflammation-induced atherosclerosis, arteriolar dysfunction, blood vessel thickening, body fluid retention, and a BBB and blood-cerebrospinal fluid barrier disintegration[3]. Vascular risk factors, such as hypertension, hyperglycemia, hyperlipidemia and blood vessel occlusion induce vasculitis, marked by inflammation and restricted blood vessel circulation. These pathological features cause neuronal damage and changes in shape and organization of blood vessels, inducing blood vessel fibrosis, indicative of adaptive immune response activation[19]. The extracellular matrix, together with cerebrospinal fluid and interstitial fluid balance, sustain nutritional needs of the brain and remove metabolic wastes as well. A change in this cerebral homeostasis stimulates aberrant immunological signals, causing brain and white matter (comprising axon and myelin) oedema, as evident from MRI and histological procedures. The alteration in blood flow and blood vessel integrity deregulate oxygen supply to the brain and also stimulate macrophage invasion and glial activation. The vascular changes promote reactive oxygen species generation and release of undesired proteins, such as matrix metalloproteinases (MMP), MMP-2, MMP-3 and MMP-9. These released components damage the extracellular matrix, induce vessel wall remodelling, disrupt tight junction protein functioning, and an ultimate BBB and white matter breakdown. Hypoxia is also another key factor that enhances the release of inflammatory MMPs, as observed in bilateral common carotid artery occlusion and spontaneously hypertensive stroke-prone situations[20-22]. Alvaro-Gonzalez et al[23] reports an important link between vascular injury and serum levels of pro-inflammatory cytokines and the C-reactive proteins that function as acute phase reactants and biomarkers for systemic inflammation. Interleukin-1 (IL-1) promotes attachment of leukocytes and inflammatory cells to the microvessels. The cytokine triggers a cascade of related pro-inflammatory cytokines and up-regulates leukocyte migration. This IL-1-induced activity aggravates arterial re-occlusion, thrombosis and neuronal injury during vascular dementia[24,25]. An increased IL-18 has also been referred in relation to cerebrovascular dysfunctions, where apoptotic caspases function as key mediators. This feature accompanies diverse PRR signaling pathways and generation of inflammasomes. In fact, the inflammasome and pro-caspase complex functions as a vital signal for the inflammatory cascades,

promoting plasma membrane disruption. Cerebrovascular abnormalities and inflammation also involve the up-regulation of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Vascular dysfunction also has a key link with Nucleotide-binding oligomerization domain that stimulates inflammasome formation, K+ efflux and caspase cleavage. An upregulated vascular endothelial growth factor induces angiogenesis and inflammation, which synergistically dysregulates immune responses and cerebral vasculature[26,27]. An enhanced serum *α1-antichymotrypsin* that serves as an acute phase inflammatory molecule also enhances vascular injury-induced cognitive impairment[28].

Receptor for advanced glycation end products (RAGE), that undergoes activation in chronic cerebral hypoperfusion and vascular damage, is abundantly present on the microglia and neurons in the hippocampus, medial temporal lobe and frontal and marginal gyrus region of the brain. RAGE serves as a key factor that connects several cerebrovascular events, particularly in relation to inflammation[29]. RAGE induces transcriptional activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which enhances pro-inflammatory cytokine and inflammasome levels and stimulates increasing inflammatory signals[30]. The RAGE-NF-κB cross-talk culminates with the activation of IκB kinase that phosphorylates IκB and inhibits the progression of NF-κB pathway. RAGE also activates the Toll-like receptors (TLRs) that are generally abundant in macrophages and dendritic cells and link up innate and adaptive immunities[31]. Moreover, RAGE stimulates the phosphorylation of phosphoinositide 3-kinases (PI3K)/Akt, Jun-N-terminal kinase (JNK), p38 and extracellular signal-regulated kinases (ERK) pathways that ultimately promote vascular stress-induced inflammation and dementia. A cross-talk between these signaling pathways stimulates the undue activation of microglia, astroglia and macrophages in the brain, leading to endothelial and neuronal degeneration and BBB damage. RAGE participates in preventing cerebral clearance of Ab that forms the key pathological hallmark of AD[32]. The increased Ab deposit not only causes cognitive dysfunction, but also stimulates the generation of IL-1, IL-6 and TNFs, and the propagation of RAGE-initiated vascular dementia[33,34].

Strikingly, MRI detected inflammation and forebrain white matter damage in association with age-dependent myelin defects, axonal loss, vascular degeneration, cognitive impairment, and dementia (VCID). VCID involved a swelling and discontinuity in the myelin sheath, which influenced normal neuronal action potential, synaptic transmission and neuronal functions. A study in rhesus monkey showed a link between VCID and inflammation, reduced myelin repair, microglial activation, defective perivascular lymphatic clearance, hemoconcentration, inadequate oxygen delivery, impaired vasodilation, and thrombosis. These inflammatory reactions aggravated cerebral small vessel disease-induced deficits in cognitive-behavior, rationality, precision, comprehension, planning, decision making, and the overall functioning of brain[35].

Inflammation, intra-cranial atherosclerosis and atherogenesis are genetic risk factors for cerebrovascular diseases. The interleukins, mainly IL-6 activated acute-phase proteins and stimulated the vascular dyshomeostasis. The excess blood coagulation enhanced endothelial cell-cell adhesion and BBB damage. Genetic factors represent key determinants of inflammation and vascular damage risks, as evident from wide variations among whites, blacks, Japanese and other population[36]. Polymorphisms of inflammatory markers even worsened pathogenesis of demyelinating and neurodegenerative disorders, traumatic brain injury and ischemic stroke. These factors are closely associated with age-related vascular disorders, such as, hypertension, hyperglycemia, coronary heart diseases, depression, electrolyte imbalance and other acute vascular events[37]. An increased NOD-like receptor-induced stimulation of nucleotide-binding oligomerization domain (NOD)-, C-terminal leucine-rich repeat (LRR)- and pyrin domain-containing protein 3 (NLRP3) inflammasome activation in the endothelial cells influenced the vascular events. Additionally, hypercholesterolemia, reactive oxygen species and reduced endothelial nitric oxide synthase levels culminated in coronary and cerebral endothelial dysfunction[38]. The secreted adipokines from adipose tissues also activated inflammasomes, which led to smooth muscle deposition and thickening of the aortal intima and atherosclerotic arteries, causing aberrant vasculogenesis[39]. An IL-1-mediated granulocyte induction and confinement into cerebral ventricles promoted an aberrant transendothelial granulocyte migration, which then exuded proteases and neurotoxicants towards neuronal damage and death.

A combination of inflammasome-induced features in the endothelial cells, neutrophils and glial cells actually appeared responsible for the cerebrovascular injury and disease[18]. During ischemic conditions, the coagulase-induced platelets increased NLRP3 and apoptosis-associated speck like proteins containing a caspase recruitment domain[40,41]. In fact, a cross-talk between platelets and immune cells triggered leukocytoclastic vasculitis as a syndrome for cerebrovascular dysfunction and dementia. In type 2 diabetes, marked by microvascular difficulties, enhanced expression of monocyte-derived macrophage and related gain-of-function SNP in the NLRP3 gene upregulated inflammation[42]. Similar sequence of events has been reported in artherosclerotic lesions, where the purinergic receptor, P2X7, activation of inflammasomes and phosphorylation of interferon-induced protein kinase R stimulated metabolic activation of inflammatory complexes. These events further induced metaflammasome formation, particularly during atherosclerotic plaque formation, apo-lipoproten E-deficiencies and disturbed fat metabolism[43]. Moreover, hyperlipidemia and obesity promoted acetylcholine and endothelium-dependent aortic relaxation, phagocyte accumulation, tunica intima density and mitochondrial loss[44]. Traumatic brain injury and stress induced the neuronal generation of inflammasomes, with a simultaneous increase in immuoreactive NLRP1 and interferon-inducible protein AIM2. The vascular damage resulted in dysregulated immune responses, loss in cellular integrity and inflammation-induced programmed neuronal death[45]. Along with this, an increased neuronal expression of the Alanine-Serine-Cysteine-1 transporter adversely affected synaptic functions *via* altered glycine-serine homeostasis in the brain. The astrocytes also activated NLRP1, NLRP2, NLRP3 and AIM2 inflammasomes in the amygdala, and stimulated generation of pro-inflammatory cytokines[46]. Additionally, potassium ion flux and the astrocytes and neuronal expression of gap junction protein, pannexin 1, and P2X7 purinergic receptor stimulated extracellular ATP-induced inflammasome activation[47]. Hence, specific NLRP3 silencing in glial cells and suppression of P2X7 receptor protected against adverse neurological consequences in animal models of brain edema[48]. Additionally, enhanced inflammasome levels reduced the expression of mitochondrial uncoupling protein-2, which hindered the protective role of astrocytes against oxidative stress and dysregulated oxidative phosphoryation[49]. At the same time, augmented oxidative stress and mitochondrial loss stimulated inflammasome-induced adverse effects and neurodegeneration, following subarachnoid and intracerebral haemorrhages and cerebral aneurysms (Figure 2). Here, the restoration of mitochondrial membrane potential and oxidative functions attenuated neutrophil recruitment to

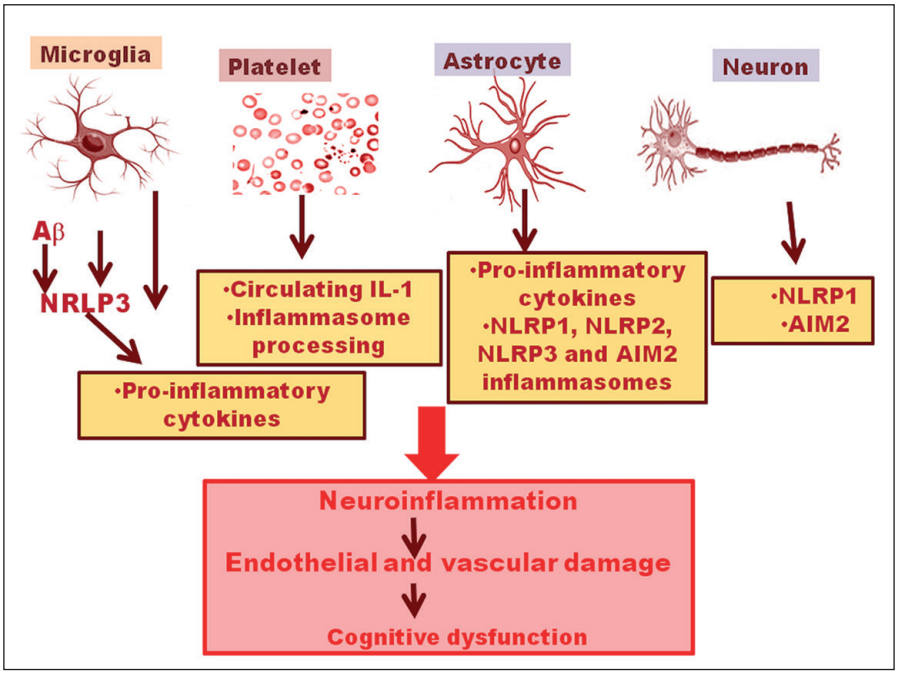

Figure 2. Brain cells and inflammation in vascular dementia. Microglia, platelets, astrocytes and neurons generate inflammasomes and pro-inflammatory cytokines as key pathways for neuroinflammation, endothelial damage and vascular dysfunction.

the site of inflammation, modulating the innate and adaptive responses. This validated the strong inter-relationship between inflammation and oxidative damage in the brain cells during cerebrovascular injury and dementia[50,51].

Autophagy and Vascular Dementia

Autophagy is a catabolic process that involves autophagosome and lysosome-dependent turnover of degraded proteins, cellular bodies, foreign components, and organelles of the body. It maintains cellular homeostasis in vascular diseases[52]. Autophagy plays a key role in sustaining vascular integrity, and an aberrant autophago lysosome formation promotes vascular degeneration, aging and related pathological conditions[53]. Vascular dementia and associated cognitive failure result from hypoxia, ischemia, excitotoxic cerebral stimuli, cerebral hypoperfusion, and brain hemorrhage. These pathologic conditions are typically regulated by interconnected and rapidly activated neuronal autophagy and AKT/cAMP Response Element-Binding Protein pathways. The two signaling mechanisms together further sustain homeostatic response and play a pro-survival role in the neurons. However, excessive autophagosome and autophagic vacuole accumulation and Microtubule-associated protein 1A/1B-light chain 3 (LC3)II/I lipidation at the site of apoptotic neurons are indicative of the neurodegenerative effects of abundant autophagic structures. In fact, it has been shown that a controlled autophagy process is vital for neuronal homeostasis, while an abundant or even inadequate autophagy is critical for neuronal dyshomeostasis. This autophagic neuronal cell death often appears as a key reason for loss in cytoplasmic matrix and cellular structures[54]. Vascular dementia involves the deposition of abnormal proteins, lipids and clots in the brain, and a regulated autophagic degradation prevents these atypical vascular accumulations and maintains normal vascular biology[1]. Vascular dementia often results from cerebral amyloid angiopathy, where a dysregulated autophagic process promotes amyloid plaque formation at the cerebral arteries, decreases clearance of abnormal protein aggregates and blood vessel collapse[55]. The oxidized lipids and amyloid beta peptides promote macroautophagy and phagophore formation, triggering an autocrine/paracrine exchange of vasoactive components across the endothelial cell layers[56].

Chronic cerebral hypoperfusion induces vascular dementia, and an activated autophagy triggers pathogenic processes in the brain and loss in synaptic activity[57]. Chronic cerebral hypoperfusion and subsequent vascular pathological manifestations also related with an increased hippocampal LC3-II/LC3-I levels. The 3-methyladenine or wortmannin-mediated autophagy inhibition restored normal synaptic remodelling and growth, particularly within the hippocampus that governs synaptic size distribution and memory[15,57]. Vascular dementia exhibited a reduced hippocampal expression of the calcium-bindin Synaptophysin (Syn) and Postsynaptic density protein-95 (PSD-95) that regulate synaptic functions and synaptic transmission and growth. The autophagy inducer, rapamycin, augmented the loss in Syn and PSD-95, aggravating vascular dementia-induced changes in the synaptic and hippocampal plasticity. Hence, blocking the autophagy process not only reduced autophagosome levels (as evident through electron microscopy) and neuronal damage, but also attenuated cognitive dysfunctions in vascular disorders. Corroborating these observations, an increased hippocampal expression of the autophagic marker Beclin-1 and the lysosomal enzyme cathepsin-B strongly stimulated the generation and progress of vascular dementia[15].

A reduced cerebral circulation during chronic cerebral hypoperfusion induces mitochondrial loss and dysfunction, enhancing oxidative stress levels that form key reasons for the astrocyte and neuronal death in the brain. Moreover, undue reactive oxygen species generation stimulates the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway of autophagy regulation, where suitable antioxidants play a key neuroprotective role[58]. Autophagy often played a protective role in vascular dementia, where treatment with the antioxidant, resveratrol, inactivated AKT and mTOR, along with the expression and phosphorylation of their downstream Ribosomal protein S6 kinase beta-1 (S6K1) and Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1)[59]. Vascular dementia also upregulated oxidative stress-induced phosphorylation of AKT and mTOR in a Bilateral common carotid artery stenosis (BCAS) animal model. The dephosphorylation of phosphatase and tensin homolog (PTEN) actually appeared responsible for activation of AKT (thr308) and mTOR. Furthermore, antioxidants caused hippocampal recovery in the BCAS model via reduction in PTEN and Raptor levels that promoted autophagy and regulated the mTOR pathway. An L-carnitine-induced axonal plasticity and decreased cognitive dysfunction

involved the participation of a controlled Pten/Akt/mTOR pathway following chronic cerebral hypoperfusion. It has been presumed that a reduction in mTOR actually suppressed the neuronal autophagy process in rats, which culminated in vascular dementia. The LC3 and autophagy adaptor, P62 that functions as an autophagic flux indicator exhibited an increase in both BCAS and antioxidant+BCAS model groups. However, P62-dependent Phosphoinositide-dependent protein kinase 1 (PDK1) demonstrated an up-regulation in BCAS+antioxidant model, thereby reducing neuronal apoptosis[60]. The protective role of PI3/AKT pathway against an attenuated Mir-21-mediated hypoxia/regeneration injury has even been reported. This miR-23b targeted potential sequences on the 3′-untranslated region of the autophagic marker, ATG12, that binds with the anti-apoptotic protein, Bcl2, and promotes neuronal cell death. The miR-96 even underwent an increase in the brain during chronic cerebral hypoperfusion, while miR-96 inhibition *via* normal expression of mTOR protected against neurobehavioral impairments[61] (Figure 3).

Autophagy plays an important role in sustaining BBB integrity, and a middle cerebral artery occlusion/reperfusion model of vascular dementia showed an enhanced endothelial cell autophagy, reduced oxidative stress and a restored expression of the tight junction-associated proteins, claudin and occludin, in the ipsilateral hemisphere[62]. The animals exhibited a decrease in P62 cargo protein, that inversely marks autophagic flux, and increase in cathepsin and LAMP1 that are usually involved in the degradation and processing of lysosomal proteins and in lysosome phagosome fusion[63,64].

Autophagy plays an ameliorative role in ischemic pre-conditioning, particularly in situations of severe cerebral damage. Here, 3-MA not only inhibited the dissemination of LC3-II from cytosol to granular vesicles, but also enhanced Beclin-1 level and blocked the autophagy-mediated protection against BBB leakage and reduction in oxidative stress. Truly, the study enlightened an intricate cross-talk among the endothelial and neuronal cells, where autophagy played a key role in inducing neuroprotection in conditions of cerebral ischemia and related vascular dementia[62]. A similar protective function of autophagy against BBB disintegration and in regulated cerebral circulation was also reported in an aneurysmal subarachnoid hemorrhage model of vascular dementia[65].

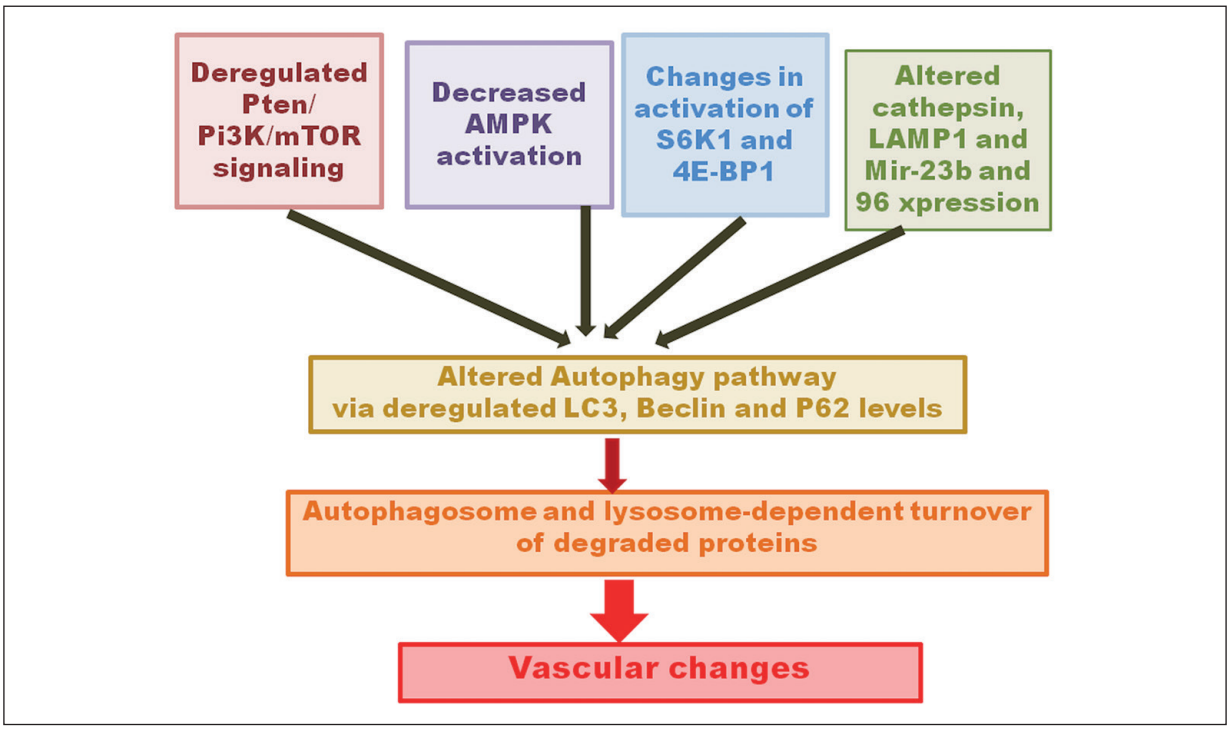

Figure 3. Factors inducing autophagy in vascular dementia. Altered autophagy pathways deregulate LC3, Beclin and P62 expression and modulate autophagosomal and lysosomal degradation in the cerebrovascular system.

Apoptosis and Vascular Dementia

Ependymal leakage, disrupted interstitial fluid flow, vasogenic perivenular white matter swelling and lesions, and Aβ dispersal and accumulation along perivascular spaces play an important contributory role in enhancing apoptosis and vascular resistance in ischemic dementia. Ischemic infarction and vascular dementia entail predominant depletion of oxygen supply in specified brain regions, causing axonal injury, apoptotic neuronal cell death, and ultimate neurodegeneration[66]. In fact, it has been recognized that cerebral neuronal apoptosis occurs subsequent to axonal loss in white matter, due to the destruction of the afferent nerve cell connections or retrograde neuronal decay[67]. MRI data showed the presence of lacunar infarcts, microhemorrhages and blood vessel rupture in the close proximity of apoptotic cells of deep white matter, which ultimately result in cognitive impairments. The electron-dense pathognomonic osmiophilic granular material lining the small arteries and capillaries at the vicinity of damaged smooth muscle cells causes malfunctioning of the blood vessel walls. It also reduces basal perfusion of the cutaneous microcirculation and cerebral hemodynamic reserve that triggers the process of subcortical ischemic hemorrhage[68,69]. A strong correlation has been demonstrated between neuronal apoptosis, characterized by increased activated caspase-3 expression, and death of pyramidal neurons. This leads to distinct subcortical protrusions in layers III-IV of the cerebral cortex, proximal white matter lesions and axonal degeneration in the subcortical fibers[67]. Vascular damage are also associated with cortical apoptosis, which showed signs of vacuolar degeneration, dark pyknotic nuclei and microinfarcts. This resulted in white matter damage, and an ultimate manifestation of memory loss and dementia[70]. Neuronal apoptosis and vascular damage comprise two steps. The primary process involves a programmed, rather than progressive cell death, and the second step is marked by irreparable DNA fragmentation. The changes in nuclear and cytoplasmic architecture are followed by cortical neuronal atrophy and reduction in cortical and overall brain volume. A number of apoptotic glial cells and axonal swellings in the edematous white matter are observed at the cortico-subcortical region, and at a remote distance from the focal subcortical white matter lesions. A decrease in cortical gray matter has also been reported in vascular dementia, and especially in subcortical ischemic vascular disorders, where anti-apoptotic drugs played a key role in attenuating the features or progression of neuronal apoptosis and vascular damage[67,71].

A marked link between vascular damage in mini-stroke or early recurrent ischemic stroke and mutations in Notch3 gene that are located in the vascular smooth muscle cells has also been reported[72], resulting in increased apoptosis and reduced cell survival. The mutations occur at the cysteine residues of epidermal growth factor-like repeats in notch gene cell receptors that participate in signaling pathways of apoptosis, promoting arteriopathy, brain infarction, cognitive impairments and dementia. In fact, a non-physiological acquisition of mutated Notch3 ectodomains along the vascular smooth muscle cells is a key to aberrant Notch functioning and reduced cell survival. These features are associated with arterial pathology, degeneration and subsequent loss of vascular smooth muscle cells of the intracranial vessels and susceptibility to stroke. This also accompanies a gradual stiffening and fibrosis of the arterial wall, along with smooth muscle cell contraction and generation of parenchymal arterioles[73]. The mechanism governing the link between apoptosis and Notch signaling as a protective factor against vascular damage stems from the concept that Notch3 causes a stimulation in Cellular (FADD-like IL-1β-converting enzyme, FLICE)-inhibitory protein (c-FLIP) that restricts Fas ligand-mediated apoptosis. Typically, ligand-induced activation of Fas triggers the recruitment and stimulation of apoptosis Fas-associated death domain proteins. It also involves c-FLIP and Notch-mediated modulation of caspase-3, caspase-7, and caspase-8, cleavage. Conversely, the Fas resistance phenotype upregulates the anti-apoptotic proteins, such as c-FLIP, Bcl-2 and c-IAP-1 in the cerebrovascular smooth muscle cells. In fact, Fas-mediated apoptosis has a vital contribution in cerebrovascular smooth muscle cell pathogenesis, where a cross-talk between ERK/MAPK and apoptotic pathways modulates the process of atherogenesis and vascular remodeling[74,75]. An intricate link between the c-FLIP and ERK/MAPK signal transduction cascade has also been reported, where the former undergoes up-regulation in the intima and media as a downstream effector following coronary arterial injury and adventitial remodelling[76]. It has also been suggested that a direct binding of the Notch3 receptor with ERK-related molecules, or a Notch-induced indirect autocrine/paracrine activation of ERK and epidermal growth factors

may have a key role in suppressing vascular smooth muscle cell apoptosis. Reduced expression of pro-apoptotic factors and accelerated expression of anti-apoptotic factors in the vascular smooth muscles appeared critical in diminishing vascular dementia[77]. Nonetheless, it has even been observed that lymphocye apoptosis was much greater in the amyloidogenic pathway of AD compared to vascular cognitive impairments, probably owing to a reduced calcium sensitivity following mitogenic response[78].

Endogenous nitric oxide and a dysregulated expression of Nitric oxide synthase (NOS) at the early stages have a key role in apoptosis and pathogenesis of cerebral ischemia. Excess endothelial and inducible NOS augment cerebral brain injury, where the former participates in the evolution and development and the latter as a mediator of cerebral ischemia and cognition loss[79]. The endothelial cells sustain the BBB integrity, and their apoptosis results in the disintegration of BBB matrix, exacerbating the process of vascular pathogenesis. A typical link between amyloid pathology and cerebrovascular lesions has also been reported, particularly in relation to endothelial NOS and apoptosis. An increased expression of the tumor suppressor protein, P53, that regulates endothelial cell and vascular smooth muscle cells of the brain has been observed in close association with neuronal Ab peptides in animal studies of AD+vascular dementia. Upregulated eNOS generation and an ultimate DNA damage in the cerebral vessels appeared as a central cause for neurite degeneration, death of smooth muscles, and vasculopathy in the leptomeninges. Oxidative stress is also a key feature of cerebral ischemia disease, and the combination of endothelial NOS and reactive oxygen species generated an aberrant breakdown of lipids. This caused the deposition of toxic products and also promoted DNA damage and programmed cell death[80].

The excitotoxic calcium/calmodulin pathway in association with eNOS promotes neuronal cell death. In fact, increased release of the pathological glutamate amino acid stimulated Ca2+ overload, and the subsequent Ca2+/calmodulin (CaM)-dependent protein kinase II (CaMKII) mediates physiological excitatory glutamate signals. This increased glutamate excitotoxicity induces neuronal apoptosis, which triggered a loss in synaptic plasticity, long-term potentiation and learning-memory abilities[81]. CaMKIIα forms around 2% of the total hippocampal proteins[82], and the autophosphorylated CaMKIIα promotes detrimental cellular calcium signalling in cerebral ischemia, cerebrovascular disorders and cognitive impairments[83-86]. The CaMKII augments Ca^{2+} burden through the α or β subunits of the L-type voltage dependent Ca^{2+} channels, and undergoes a direct binding with connexin hemichannels that offer pathways for cellular connectivity with the extracellular surrounding[87]. Hence, this CAMK-connexin interaction disrupts normal neuronal homeostasis, affecting neuron-glia cross-talk, which also forms a key reason for glutamate-induced excitotoxicity and neuronal cell death. Another key role played by CAMKII in vascular dementia comprises the increased phosphorylation of neuronal voltage-insensitive acid-sensing sodium channels. These pathological cascades deregulate NO production, vasodilation, and mediates cerebrovascular responses during injury and cerebral damage. Moreover, CaMKII promotes nuclear translocation of cytoplasmic polyadenylation element binding 4 (CPEB4) that stimulates memory storage and synaptic plasticity, exacerbating neuronal cell apoptosis in cerebrovascular disorders[88,89]. Moreover, an enhanced intranuclear localization of apoptosis-inducing factor triggers caspase-independent programmed neuronal cell death involving chromatin condensation and DNA fragmentation in vascular

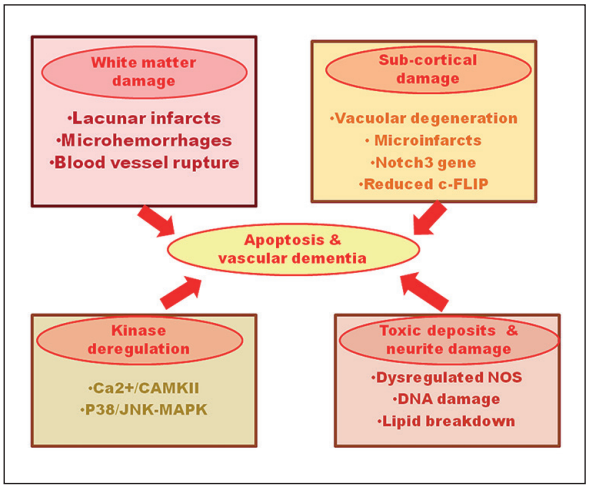

Figure 4. Factors promoting apoptosis in vascular dementia. Damage to white matter, sub-cortical region and neurites in association with altered kinase pathways increase apoptosis and cell death in the cerebrovascular system.

dementia[90] (Figure 4).

Demyelination of the white matter, due to oligodendrocyte apoptosis and atrophy comprise characteristic features of vascular dementia, as observed in animal models. In fact, aging and vascular diseases decrease chances of myelin regeneration by the oligodendrocytes and enhances white matter hyperintensities[35]. The process also accompanies axonal disintegration, astrocytogliosis, microglial activation and oligodendrocyte death in the frontal lobe, followed by their effects on the parietal, temporal and occipital lobe. These features of severe white matter damage not only culminate in dementia, but also manifest optical, retinal, and visual damages, as evident from MRI[91].

Notably, the Apoptosis signal-regulating kinase 1 (ASK1), a member of the MAPK family and activator of the p38 and C-JNK-MAP kinase, shows significant participation in stress, with a key role in angiotensin II-induced endothelial cell apoptosis and damage[92,93]. The process of chronic cerebral hypoperfusion and subsequent white matter lesions, involving claudin and occludin-induced BBB and endothelial tight junction damage, also comprised an oxidative stress-induced ASK1-P38 signaling pathway. This feature was particularly observed within the corpus callosum and at the early stages of the disease. NADPH oxidase-mediated superoxide radical generation actually stimulated ASK1 in cerebral hypoperfusion-triggered memory loss. A pro-inflammatory, TNF-α appeared up-stream of the ASK1 activation and tight junction damage in cases of cerebral hypoperfusion. Concurrently, inhibiting ASK activation restricted features of memory loss in vascular dementia, as evident from BCAS mice models[94].

Concurrent Inflammation, Autophagy and Apoptosis in Vascular Dementia

A synchronized activation of autophagy, inflammation, and apoptosis is functionally involved in development and pathogenesis of vascular dementia, characterized by the simultaneous stimulation of LC3-II and beclin-I protein, NLRP3, IL-1 and caspases. Often, the three processes also undergo activation in a sequential and inter-dependent manner. Iron dysregulation also plays a critical role in vascular dementia, with the participation of both autophagy and apoptosis in the hippocampal neurons[95]. Here, the permanent BCAO model demonstrated enhanced iron deposition and dysregulation of iron homeostasis, along with enhanced hippocampal expression of iron transport related molecules (transferrin receptor-3 and divalent metal transporter-1). This increased iron accumulation appeared as a key cause for augmented expression of autophagy regulators and markers, AMPK, Beclin1, LC3, and autophagosomes. The augmented hippocampal iron content resulted in upregulated Bax and decreased Bcl2 levels, culminating in Morris Water Maze test-detected learning-memory impairments[95]. A direct link between inflammation and apoptosis has also been observed in vascular dementia, where the knock-out of TLR4 and suppression of NF-κB signaling abrogated apoptosis and downregulated oxidative stress. Reduced inflammatory events decreased number of errors and regulated the latency period in neurobehavioral tests in a cerebral small vascular disease mouse model of carotid occlusion[96]. Furthermore, a monoclonal antibody-mediated inhibition of IL-1 not only blocked its own expression, but also reduced caspase levels and enhanced anti-apoptotic Bcl2 protein expression, together with an attenuated P38 MAPK activation that stimulates the progression of vascular dementia[97].

Conclusions

Vascular dementia appears subsequent to multiple factors, due to primary damage to the microhemodynamics and alteration in blood vessel thickening and dysfunction. Several targets in inflammation, autophagy and apoptotic pathways, such as autophagy breakdown products, intracellular pathogens, damaged mitochondria, NLRP3 inflammasomes and detrimental apoptotic adducts form key molecules that trigger pathogenesis of chronic brain hypoperfusion. They finally induce defects in neuronal crosstalks and prompt memory loss. Hence, therapeutic targeting of the transducer and transcription proteins in these signaling pathways could reduce synaptic and neuronal damage and associated deleterious impacts of vascular dementia. Microarray, proteomic and metabolomic analyses of the signaling pathways may offer new avenues for restoring normal neuronal network and blocking the vital nodes promoting vascular pathogenesis. Further, exploratory research on the participation of inflammation, autophagy and apoptosis in vascular neurodegeneration may identify common and diverse mechanisms

underlying neuronal death. These targets in the molecular mechanistic pathways could serve as novel markers for the vascular disorders. Developing therapies for vascular dementia is a genuine challenge, and hence, utmost cautiousness is warranted in designing therapies targeting vascular disease initiation and progression. This would help in sustaining the normal and undisrupted physiological features of the neuronal and synaptic networks.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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