Vascular Dementia and Crosstalk Between the Complement and Coagulation Systems

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Vascular Dementia (VaD) is a neurocognitive disorder caused by reduced blood flow to the brain tissue, resulting in infarction, and is the second most common type of dementia. The complement and coagulation systems are evolutionary host defence mechanisms activated by acute tissue injury to induce inflammation, clot formation and lysis; recent studies have revealed that these systems are closely interlinked. Overactivation of these systems has been recognised to play a key role in the pathogenesis of neurological disorders such as Alzheimer’s disease and multiple sclerosis, however their role in VaD has not yet been extensively reviewed. This review aims to bridge the gap in knowledge by collating current understanding of VaD to enable identification of complement and coagulation components involved in the pathogenesis of this disorder that may have their effects amplified or suppressed by crosstalk. Exploration of these mechanisms may unveil novel therapeutic targets or biomarkers that would improve current treatment strategies for VaD.

Keywords: vascular dementia (VaD), complement, coagulation, crosstalk, small vessel disease

INTRODUCTION

Vascular Dementia (VaD) is a progressive neurocognitive disorder with classic cerebrovascular and cardiovascular risk factors. Crosstalk between the coagulation and complement systems has gathered increasing scientific attention in recent years, however there is still much to uncover especially regarding the impact of these systems on different disease states such as VaD. The understanding of the interaction between coagulation and complement in VaD is lacking and there are currently no reviews available that discuss them side-by-side. This review aims to bridge the gap in knowledge by collating current understanding of VaD to enable identification of complement and coagulation components involved in the pathogenesis of this disorder, that may have their effects amplified or suppressed by crosstalk. Improved understanding of underlying mechanisms may ultimately aid in improving treatment options available for VaD.

VaD is caused by reduced blood flow to the brain, and can present with behavioural symptoms, locomotor problems, and loss of executive function (1, 2) (Figure 1). VaD is the second most common type of dementia, accounting for roughly 15% to 20% of dementia cases in North America and Europe (3). Subtypes of this condition are defined by the cause and nature of vascular pathology, number of intracranial vessels involved, anatomical location of tissue changes, and the time after the initial vascular event (2). These subtypes include post-stroke dementia, multi-infarct dementia, subcortical dementia, mixed dementia, and CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (1). There are currently no specific medications approved for the treatment of VaD (4). Underdiagnosis of VaD, lack of treatment...
options and an increase in the population suffering from VaD risk factors emphasise the necessity for research and treatment development for this disease. Clinical trials of the acetylcholinesterase inhibitor Donepezil, currently indicated for Alzheimer’s disease were not promising in VaD, with the drug found to be much less effective in VaD than in Alzheimer’s disease (5), with patients attaining small improvements in cognitive function, but no improvement in global functioning that helps day-to-day life. Moreover, since definitive confirmation of VaD is only possible post-mortem, it has been difficult to ascertain the exact prevalence of VaD worldwide due to varying diagnostic criteria and very few population-based cohort studies available on the subject (6, 7).

For neuropathological diagnosis of VaD, key cerebrovascular lesions need to be present such as ischaemic infarcts (necrosis due to blood vessel blockage), haemorrhagic infarcts (bleeding in or around the brain), lacunar infarcts (small infarcts in the deep tissues of the brain from penetrating artery occlusion), and microinfarcts (microscopic lesions <1 mm in diameter) (8–10). Lacunar infarcts and microinfarcts are the most common type of infarct found in VaD (11). However, regardless of the type, accumulation of infarcts increases the likelihood of dementia (12). Other key neuropathological changes include atherosclerosis seen in medium to large sized arteries at the base of the brain with plaques containing lymphocytes and macrophages that have begun to destroy the vessel wall (later stage plaques may have necrotic cores, cholesterol clefts and calcification), arteriosclerosis seen in small arteries and arterioles (very common and early change), and other microangiopathies (2, 12–14). However, a robust internationally accepted set of neuropathological criteria for VaD is still needed.

Cerebral small vessel disease (SVD) is not only associated with an increased risk of stroke (15–17), but data from 13 different studies on 12,931 patients across Western Europe and the USA found SVD as the most common cerebrovascular pathology in clinically diagnosed VaD followed by large-vessel disease (2, 18–30). SVD is the most common and important vascular cause of VaD, also referred to as subcortical VaD (31, 32). SVD causes slow progressive changes to the brain due to diseased arterioles and micro-vessels but can also affect larger vessels and veins (33). SVD often coexists with atherosclerosis of the extracranial vessels and cardioembolic disease, which all associate with VaD (34). In SVD, vessels undergo progressive age-related changes such as fibrinoid necrosis (necrosis of vessel wall), hyalination (thickening of vessel wall), intima thickening, arteriosclerosis, astrocytic gliosis, and expansion of perivascular spaces, which cumulatively all decrease perfusion and result in lacunar infarcts and microinfarcts (2, 33, 35, 36). These lesions arise from a loss of blood flow response, since the thickened and less elastic vessel walls cannot respond to fluctuations in blood pressure by dilating or constricting to maintain constant tissue perfusion (33, 37, 38). This leaves brain tissue vulnerable to infarction, especially the deep cerebral structures and white matter since these are supplied by end arteries with almost no anastomoses to compensate (2). It has been suggested that lacunar strokes are more often a result of vascular degeneration, rather than arteriole occlusion as originally assumed, however more research is needed to confirm this (39).

**RISK FACTORS OF VASCULAR DEMENTIA**

Many factors have to date been linked to increased risk of developing VaD (Figure 1).
Diabetes mellitus has been found to double the risk of dementia and has been established as a clear risk factor for VaD (40). Having diabetes in midlife (<65 years) is a stronger risk factor for dementia than in later life (41). In addition to duration of diabetes, the occurrence of peripheral vascular disease is also an independent risk factor for dementia (42). The link between diabetes and VaD is not surprising since diabetes increases the risk of stroke, lacunar infarcts and vascular damage, which inevitably increase the risk of VaD (1, 43, 44).

Hypertension
Hypertension is a risk factor for VaD, especially if untreated. It has been reported that the use of antihypertensives to control blood pressure in midlife reduces the incidence of dementia in later life (45–48). Uncontrolled hypertension precedes white matter lesion development and worsens VaD disease progression (49). Conversely, other studies have found an association between low blood pressure and dementia risk, with the Framingham Study finding no association between blood pressure and cognitive performance (50–52). Therefore, it is unclear whether decrease in blood pressure is a side effect of dementia or a decline in blood pressure in later life after having high blood pressure in midlife is a sign of dementia to come (1).

Metabolic Syndrome
Metabolic syndrome is characterised by a combination of several metabolic derangements that include hypertension, dyslipidaemia, central obesity, and insulin resistance (53). A cohort of 7,087 participants from the French Three-City study showed that baseline metabolic syndrome in patients >65 years increased the risk of incident VaD over four years (54). Triglycerides (45% increase) and diabetes (58% increase) in particular were significantly associated with an increase in all-cause dementia (54). Metabolic syndrome also doubles the risk of developing dementia in individuals with mild cognitive impairment (55). However, the exact role of metabolic syndrome in cognitive dysfunction is still unclear due to age having varying effects on the syndrome's impact on cognitive decline (1).

Age
The cerebrovascular endothelium becomes increasingly permeable with age, with blood-brain barrier endothelial integrity decreasing progressively after the age of 70, and such changes are commonly seen in VaD patients (31, 56). Even people without dementia in the general population have an increasing prevalence of cortical infarcts, lacunar infarcts, and microbleeds as they get older (57–59). Despite these infarcts and microhaemorrhages or microbleeds being common in elderly patients with normal cognition, these lesions are associated with reduced cognition and executive function (2, 60, 61). Microbleeds were present in 85% of patients with subcortical VaD, and are therefore likely to be a marker of SVD (62). Interestingly, age-related dementia risk has steadily decreased in Europe and North America over the past couple of decades with one possible explanation being better vascular risk factor control in mid-life, which reduces the cumulative effect experienced by the cerebrovascular system over time (63, 64).

Stroke
Post-stroke dementia is a subtype of VaD resulting from ischaemic and haemorrhagic stroke, where 10% of patients develop dementia after their first stroke and a third of patients after recurrent stroke (65). South Asians are at a particularly high risk of ischaemic stroke due to a greater burden of hypertension, diabetes, and dyslipidaemia (66, 67). Although not all stroke patients develop post-stroke dementia, recurrent stroke prevention and cardiovascular risk factor control remain the therapeutic cornerstone of preventing VaD (3) due to stroke doubling the risk of all-cause dementia (68).

Genetics
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most common genetic cause of stroke and VaD in adults (69, 70). CADASIL is the result of a mutation to the NOTCH3 gene that encodes for a transmembrane receptor crucial to blood vessel integrity (71, 72), eventually leading to dementia due to systemic vascular degeneration (73), however the exact mechanism of disease remains to be uncovered (74). CARASIL is the very rare autosomal recessive (R) form of this hereditary microangiopathy, which is caused by a mutation to the HTRAI gene encoding a serine protease (71, 75). Onset of cognitive decline and ischaemic stroke resulting from these microangiopathies characteristically begins in early to mid-life (69), however further research is still required to establish the exact mechanism that leads to VaD.

PATHOLOGY OF VASCULAR DEMENTIA
Current understanding of the pathophysiology behind SVD and thromboembolic events that lead to cerebral damage and VaD is centred around mechanisms involving hypoxia, oxidative stress, and inflammation (Figure 2).

Hypoxia
Hypoperfusion and reduced cerebral blood flow is a characteristic feature of VaD (76). Chronic hypoperfusion and thromboembolic events result in reduced cerebral blood flow and hypoxia, which aggravates oxidative stress and triggers inflammatory responses (1, 77).

The brain demands a large cardiac output to fulfil its high oxygen and metabolic demand for normal functioning, which makes this organ extremely vulnerable to hypoxic damage. The periventricular white matter, basal ganglia, and hippocampus are all highly susceptible to hypoperfusion induced lesions; additionally, poor collateral blood supply in the deep structures of the brain leave cerebral white matter very susceptible to hypoxia induced damage (78). Frontal lobe white matter myelin loss is a hallmark of VaD, and this demyelination is a result of hypoxic injury to the oligodendrocytes (79). These ischaemic lesions result in neurocognitive decline as demonstrated in rats suffering a decline in cognitive performance when cerebral blood flow was reduced (80).
Oxidative Stress

Oxidative stress refers to the excessive generation of reactive oxygen species and reactive nitrogen species that damage cellular proteins, lipids, and DNA (80). Studies indicate that oxidative stress is associated with the pathogenesis of VaD (81), which may be because the brain is relatively more susceptible to oxidative stress than other organs due to its high metabolic rate, high polyunsaturated lipid content, and lower levels of endogenous antioxidant activity and protective mechanisms (80).

Cerebral hypoperfusion-induced hypoxia can promote mitochondrial dysfunction, inhibit protein synthesis, and cause ATP depletion and ionic pump disorder (82). Mitochondrial dysfunction leads to increased reactive oxygen species production, which is problematic because of a simultaneous reduction in antioxidant production due to protein synthesis inhibition (80). This combination results in more severe oxidative damage due to the significant disruption in balance of reactive oxygen species to antioxidants, which damages vascular endothelial cells, glial cells, and neuronal cells therefore causing neurovascular uncoupling that results in a reduction in cerebral blood flow, further exacerbating this cycle (1, 80). Furthermore, reactive oxygen species react with nitric oxide to form peroxynitrite, eliminating circulating nitric oxide that is necessary for cerebrovascular functions such as vasodilation and enzymes oxidation, further disrupting cerebral blood flow (83).

Diabetes may partly increase the risk of VaD through build-up of reactive oxygen species as a result of hyperglycaemia which perpetuates this disease process (84). Similarly, hypercholesterolaemia is associated with an increase in free-radical formation and reduced antioxidant levels (81, 85). In mouse models, vascular oxidative stress disrupts the cerebral microvasculature’s ability to clear amyloid-β peptide, leading to toxic accumulation of amyloid proteins that contribute to neurodegenerative mechanisms and cognitive impairment (86, 87).

Inflammation

Tissue hypoxia triggers a series of complex molecular mechanisms inducing vascular inflammation, neurovascular unit disruption, microvascular remodelling, and dysfunction in response to tissue injury (88–90). Hypoxia-inducible factor-1α and matrix metalloproteinase-9 are released which produce free radicals, induce vasogenic oedema, degrade the blood-brain barrier and increase inflammatory factors such as interleukin 1 and 6, matrix metalloproteinase 2 and 9, tumour necrosis factor α, toll-like receptor 4 and C-reactive protein (1, 33, 91–93). These inflammatory factors aggravate white matter damage in the brain, cause neurodegeneration, cell death and neuroglial inflammation which further progress VaD development (31).

COAGULATION AND COMPLEMENT SYSTEMS IN VASCULAR DEMENTIA

The coagulation and complement systems are separate complex evolutionary defence mechanisms underpinning inflammation, clot formation and degradation to protect the host. Extensive
literature reveals important crosstalk between these two systems (94–97) which uncovers exciting therapeutic potential for pathologies resulting from overactivation of these systems, such as thromboembolic disorders associated with stroke and VaD.

The coagulation system is a series of physiological events that ensure haemostasis (stopping of bleeding) by producing a fibrin meshwork that stabilises the preliminaryplatelet plug formed at the site of endothelial damage (98). Endothelial damage exposes collagen and tissue factor, which activate platelets and the extrinsic pathway of coagulation respectively. Thrombin generated through the coagulation system converts fibrinogen to fibrin, forming the fibrin fibres mesh that stabilises the initial platelet plug (98) (Figure 3).

The complement system is key to the body's defence mechanism against pathogens as part of innate and adaptive immunities (99). Contact with pathogenic surfaces triggers a series of reactions resulting in three main outcomes: production of proinflammatory mediators, opsonisation (marking of cells for phagocytosis) and destruction of pathogenic cells via the formation of a membrane attack complex that makes pores in the pathogen cell membrane (100). Complement activation occurs through three possible pathways: classical, lectin and alternative pathways, resulting in complement activation and membrane attack complex formation (99) (Figure 3).

Coagulation and VaD
Coagulation can be activated by vascular injury caused by hypoxia and inflammation (101). Follow-up studies of the Rotterdam study in the 1990's found that dementia risk increased with elevated levels of serum fibrinogen, thrombin-antithrombin complex, D-dimer, and tissue-type plasminogen activator (102, 103). Although the authors noted that some misclassification between Alzheimer's disease and VaD may have occurred due to difficulty differentiating between the two diseases, 31 out of the 192 dementia cases in the cohort were VaD patients (103), raising concerns about the statistical power of some of these associations. Gallacher et al. also found associations between dementia risk and fibrinogen in addition to factor (F)VIII, plasminogen activator inhibitor-1, and plasma viscosity (104). Although their study was smaller than the Dutch studies and only included men, the associations were made over a much longer 17-year prospective time frame (104). It was suggested that these components increased VaD risk by altering fibrin clot formation and lysis activity through the FVIII / von Willebrand factor complex and elevated plasminogen activator inhibitor-1 (impaired fibrinolytic activity), which lead to hypercoagulability and microinfarction (104). Further systematic reviews and meta-analyses support associations between fibrinogen, FVIII, D-dimer, and FVIIIa, and von Willebrand factor in VaD patients (105, 106).

FVIII levels increase in acute stroke (107) and generally with age (108), in addition to their association with increased VaD risk (104–106). However, a recent study found no strong association between FVIIIa clotting activity and cognitive function or burden of white matter hyperintensities on magnetic resonance images (109). Although this study did not specifically look at VaD, as previously discussed, white matter damage is one of the hallmarks of VaD and SVD (79). It is therefore possible that FVIII does not progress cognitive decline and VaD through its clotting activity, but rather through another mechanistic role that needs exploration, such as crosstalk with other systems. Thrombomodulin and tissue factor on the other hand, have been associated with the extent of leukoaraiosis (abnormal white matter) in cerebral SVD (110).

Some studies have found associations between vascular cellular adhesion molecule-1, C-reactive protein, and interleukin-6 with VaD and cognitive decline (111, 112), whilst other studies have not (103, 104). Although sample size was an issue in all of these studies, the Dutch studies had slightly more robust data due to repeats. Nonetheless, further research is necessary to establish the roles of these inflammatory markers in cognitive decline (113, 114).

Lower levels of endothelial progenitor cells are found in CADASIL patients (115), which is associated with more significant degeneration of cognitive and motor performances, possibly due to their role in maintaining normal homeostasis and structure of the endothelium (116). CADASIL patients also had significantly higher von Willebrand factor levels than controls (115), which is a marker of endothelial damage and dysfunction (117). Elevated levels of lipoprotein-associated phospholipase A2, an enzyme which influences platelet activation and inflammatory molecule production for low-density lipoproteins, have been identified as a risk factor for dementia development (118).

Finally, kinins from the kallikrein-kinin system are pro-inflammatory peptides that are important in regulating vascular permeability, oedema formation, trans-endothelial cell migration and inflammation in different organs following injury (119). Activation of FXII initiates both the intrinsic coagulation pathway and the kallikrein-kinin system when it meets negatively charged surfaces, triggering both clotting and inflammation seen in ischaemic stroke (120–123). Prekallikrein is a key component of the contact-kinin system and can activate FXII in the intrinsic pathway. Prekallikrein-deficient mice had significantly smaller brain infarctions and less severe neurological deficits due to reduced intracerebral thrombosis, with improved cerebral blood flow and blood-brain barrier function, suggesting that prekallikrein inhibition could be a potential strategy for stroke prevention (124). It is likely that these same mechanisms contribute to stroke induced VaD, suggesting that prekallikrein inhibition in humans could be a potential therapeutic target in VaD prevention.

Complement and VaD
The complement system component C3a (anaphylatoxin) has been reported to be involved in cerebral white matter injury in rats (125). Microglia are the resident macrophage cells of the central nervous system and are key to maintaining normal brain homeostasis, however chronic activation of these cells via the C3a-C3aR (receptor) pathway in hypoperfusion can aggravate white matter injury by engulfing myelin fibres, resulting in cognitive dysfunction (125). One study found that intracortical administration of a C3aR antagonist (SB 290157) resulted in reduced phagocytosis of neurones, since microglia
expressing C3aR were inactivated (126). The CODAM study found a strong positive correlation between carotid artery intima-media thickness, ankle-arm blood pressure index, and plasma C3a levels in humans (127), suggesting that C3a promotes atherosclerosis, which could contribute to the pathogenesis of SVD. Interestingly, in hyaline arteriosclerosis, inactive C3b is a major component of the hyaline material deposited in the vessel wall of arterioles, suggesting another role for the complement system in SVD pathology (36). Inhibition of mannos-binding lectin pathway offers therapeutic benefit by attenuating C3 activity after oxidative stress (128). Finally, in vitro studies and mouse models have demonstrated that C5a (anaphylatoxin) can induce the release of histones and reactive oxygen species that leads to inflammation, endothelial damage, and thrombosis (129), fitting the oxidative stress model of VaD.

Crosstalk Between the Coagulation and Complement Systems

Studies looking at the effect of complement proteins on coagulation activity, and vice versa, have identified a number of communication avenues between the systems (Figure 3). Complement protein C5a was found to increase tissue factor expression in human umbilical vein endothelial cells (130), which was supported by another study reproducing this effect in monocytes (131). This is significant because it shows that the complement system may contribute to initiation of coagulation, since tissue factor is the primary physiological initiator of the coagulation system (94). Mouse models have also indicated that C5 activation amplifies tissue factor activation on myeloid cells, whilst C3 activation helps induce platelet activation, showing that both C3a and C5a have prothrombotic roles in promoting fibrin formation (132). Plasminogen activator
inhibitor-1 is a potent inhibitor of the conversion of plasminogen to plasmin, and therefore fibrinolysis (133). C5a has been found to increase plasminogen activator inhibitor-1 expression from mast cells (134), thus preventing clot breakdown. This could explain the association between dementia and elevated plasminogen activator inhibitor-1 levels reported by Gallacher et al. (104). Additionally, assembly of the C5b-9 (membrane attack complex) on endothelial plasma membranes triggers the exposing of FVa binding sites on the membrane, therefore promoting prothrombinase complex assembly to accelerate thrombin generation (135, 136).

Conversely, studies of the influence of coagulation system activity on complement has revealed that the coagulation factors FXII, FXI and prekallikrein not only initiate the intrinsic pathway, but can also initiate the classical (antigen-antibody complex) and alternative (Factor B mediated formation of C3 convertase) complement pathways (94, 137). C3 and C5 are typically converted to their active form by C3 and C5 convertase, however studies have shown that they can also be cleaved to C3a and C5a by FXa (most potent) followed by plasmin, thrombin, FIXa, and FXIIa (138, 139).

Activity can be both stimulated and inhibited in either system by crosstalk, for example thrombomodulin in the coagulation system can downregulate complement by inactivating C3b into the inactive iC3b (140). Another example is tissue factor pathway inhibitor, which plays a role in impeding blood coagulation by preventing the activation of the tissue factor / FVIIa complex and FXa (141–144). Work by Keizer et al. has identified tissue factor pathway inhibitor as a selective inhibitor of mannose-binding lectin-associated serine protease-2, which therefore inhibited cleavage of C4 and C2 in the lectin pathway (94, 145). This may be a useful therapeutic target for VaD, as studies have suggested deficiencies of the lectin pathway have protective effects against stroke and ischaemic-reperfusion injury in mouse and human (145–148). For example, a prospective cohort study found mannose-binding lectin deficiency was associated with smaller cerebral infarcts and better outcomes following ischaemic stroke (147). Extrapolating from this, one could argue mannose-binding lectin deficiency could potentially reduce the risk of post-stroke VaD.

Finally, a positive complement-platelet activation loop exists, whereby activated platelets release complement components that promote vascular inflammation, atheroma formation and activate further platelets, which exacerbates complement activation (149–154). Future studies could investigate whether this activation loop has a role in the mechanism behind cerebrovascular inflammation and the disruption of the blood-brain barrier in VaD. Much remains to be uncovered about the crosstalk between the complement and coagulation systems in the pathogenesis, prevention, and treatment of VaD.

**CONCLUSION AND FUTURE PERSPECTIVES**

VaD is a complex neurocognitive disorder with major impact on quality of life. There is still much to learn about this disease, one of which being the role of complement and coagulation systems in the underlying mechanisms, along with crosstalk between these systems which could provide novel therapeutic targets to improve patient outcomes, fulfilling the urgent need for effective treatment strategies. Measuring serum markers of activated complement and coagulation components could also be useful for the identification of individuals at risk of cognitive decline and track dementia progression.

The link between complement, coagulation, crosstalk and VaD in this review highlights possible areas for future research that remain to be fully explored. i) What is the mechanistic link between coagulation components FVIII, FVIIa, fibrinogen, thrombin-antithrombin complex, D-dimer, tissue-type plasminogen activator, plasminogen activator inhibitor-1, von Willebrand factor and VaD? ii) What is the role of the inflammatory markers vascular cellular adhesion molecule-1, C-reactive protein, and interleukin-6 in cognitive decline? iii) Are C3α and C5α involved in white matter injury in humans? iv) Can prekallikrein inhibition reduce the risk of stroke and VaD in humans? v) What is the extent of crosstalk between all these components and how does this lead to VaD development?

Over and under activation of the complement and coagulation systems have been recognised to play a part in various diseases such as Alzheimer’s disease, multiple sclerosis, atypical haemolytic uremic syndrome, and antiphospholipid syndrome (94, 101). Therefore, the potential role of these systems in VaD should be considered. Current studies have already suggested a link between blood hypercoagulability and cognitive decline in dementia, however the statistical power of these studies is still not great enough to confirm without a doubt that the haemostatic system is part of the pathological mechanisms that lead to VaD (113). The limited data on complement and VaD emphasise the need for further research into complement components and how these could potentially be involved in driving the process of hypoxia, oxidative stress and inflammation that result in cerebral infarction. Another problem that still needs addressing is the lack of an internationally recognised standard of VaD neuropathological criteria to enable direct comparison and analysis of research (2). It is currently difficult to compare the results of studies due to varying selection criteria for patients, which means that patients that are eligible in one study are not recognised as VaD patients in another study due to differing diagnostic criteria.

**AUTHOR CONTRIBUTIONS**

MMP sourced and analysed the literature and wrote the first draft of the review. CD and RA critically reviewed the literature analysis and helped developing the manuscript. All authors contributed to the writing of this manuscript and approved the final version.

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