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Models and Mechanisms of Vascular Dementia

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Abstract

Vascular Dementia (VaD) is the second leading form of dementia after Alzheimer's disease (AD) plaguing the elderly population. VaD is a progressive disease caused by reduced blood flow to the brain, and it affects cognitive abilities especially executive functioning. VaD is poorly understood and lacks suitable animal models, which constrain the progress on understanding the basis of the disease and developing treatments. This review article discusses VaD, its risk factors, induced cognitive disability, various animal (rodent) models of VaD, pathology, and mechanisms of VaD and treatment options.

Keywords

Vascular dementia; Cognition; Multiple infarct dementia; High fat diet; Treatment

Introduction

Define Vascular Dementia

Vascular Dementia (VaD) is a progressive disease that affects cognitive abilities and is caused by reduced blood flow to the brain. VaD patients may suffer from slowed thinking, forgetfulness, depression and anxiety, disorientation, and loss of executive functions like problem solving, working memory, thinking, reasoning, judgment, planning and execution of tasks, with performance declining with increasing task complexity. VaD accounts for about 17–20% of all dementia patients making it the second leading form of dementia after Alzheimer's disease (AD), and is prevalent among the older population [1].

VaD can be caused by a reduced cerebral blood flow supplying the brain that may or may not be associated with a stroke. VaD includes the following: multi infarct dementia characterized by multiple small strokes, single infarct dementia caused by a single major

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stroke with hippocampal damage, small vessel disease (SVD) and vasculitic dementia in which patients additionally suffer from migraine like headaches caused by inflammation of blood vessels. Under-diagnosis of VaD, lack of treatment options, increasing life expectancy and a steady rise in the population suffering from its risk factors like hypertension, cardiac disease, diabetes, metabolic syndrome and stroke necessitate development of treatments for VaD; Fig 1 summarizes VaD risk factors, subtypes and characteristic features. Since, AD and VaD can have clinically similar symptoms and may coexist in many patients; the two disorders are easily confused. Hence, it is important to clearly understand the similarities and differences between VaD and AD; these have been summarized in Table 1.

Risk of vascular dementia

1) Diabetes

Diabetes has been established as a risk factor for VaD [2–5] and is reported to almost double the risk of dementia [6]. Pre-diabetes and diabetes patients also risk a conversion of mild cognitive impairment into dementia [7]. Diabetes increases the risk of VaD especially when diabetes occurred in patients during their mid life, i.e. age <65 years [2]. The risk of developing VaD was higher than AD with an average dementia onset age of 76.8 years [2]. The duration of diabetes and occurrence of peripheral arterial disease are also independent risk factors for dementia [8]. An autopsy based study [9] revealed a significant difference in patients with dementia with or without diabetes and reported that while non diabetic dementia was found associated with greater Aβ deposition characteristic of AD, diabetic dementia was associated with more micro vascular infarctions and neuroinflammation characteristic of VaD. Neuroimaging using CT and MRI has shown a clear association between diabetes and cerebral atrophy and lacunar infarcts [10]. The involvement of diabetes with VaD is not surprising given the knowledge that diabetes increases the risk for stroke [11, 12], lacunar infarction [13] and is associated with extensive vascular damage and worse outcomes post stroke [14, 15].

2) Hypertension

Increasing age (>60 years) is a risk factor for hypertension [16] which in turn is a potential risk factor for VaD [17]. Middle age (mean age 54 years) hypertension can increase the risk of VaD in late age (approximately 25–30 years later) especially if untreated and can increase hippocampal atrophy [18–21]. The impact of hypertension on VaD can be explained by several mechanisms centering around white matter (WM) damage: WM lesions in the aging non demented population has been associated with elevated blood pressure (BP); uncontrolled and untreated hypertension is a high risk factor for WM lesions and worsens VaD disease progression; blood brain barrier (BBB) compromise, vascular changes and silent strokes induce vascular and WM damage [22]. Researchers and clinical trials have reported a decreased dementia risk in patients receiving treatment for hypertension [23, 24]. While the Framingham Study [25] has indicated a lack of influence of BP on cognitive performance, other studies have reported a lowering of systolic BP in elderly patients 3–6 years prior to the onset of dementia, and >15mmHg decrease was associated with an increased risk of dementia in patients with pre existing vascular disorders or low BP [26–28]. Therefore, it is unclear if the decline in BP is a complication or side effect of dementia

and if this decline in BP after high BP in mid life can be in fact used as a predictor for dementia

3) Metabolic syndrome (MetS)

MetS is a combinatorial effect of at least three of several cardiovascular risk factors including abdominal/central obesity with large waistline, hypertension, dyslipidemia with high triglycerides or low high density lipoprotein (HDL) cholesterol, and insulin resistance i.e. high fasting blood glucose levels [29]. MetS appears to have a moderately significant effect on cognitive decline but only in patients less than 70 years [30, 31]. While 65 year old MetS patients suffer from poor memory and poor executive performance [32], in older male participants (>75 years) late life MetS could possibly induce protective effects on cognitive decline [33]. MetS and in particular high triglycerides and diabetes have been indicated to increase VaD risk over 4 years in patients of age =/>65 years [34]. While the exact role of MetS in cognitive dysfunction is unclear, a decrease in cerebral blood flow (CBF) may be responsible for loss in short term/immediate memory in late middle aged MetS patients (mean age 60.4 years) especially in those who suffer from abdominal obesity and high triglycerides level [35]. MetS increases the risk of progression from mild cognitive impairment to dementia [36] and has been associated with increased inflammation [37, 38].

Evaluation of cognitive dysfunction

Figure 2 summarizes the various aspects of cognitive dysfunction that VaD patients suffer from. The clinical diagnostic criteria for VaD include NINDS-AIREN (National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences), ICD-10 (10th revision of the International Classification of Diseases), DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) and ADDTC (Alzheimer's Disease Diagnostic and Treatment Centers), and these have been discussed previously [39, 40].

In animal models, cognitive abilities can be evaluated by a battery of functional tests including but not limited to:

1. Odor test for olfactory learning based on animals preference for new smells [41];
2. Novel object recognition test to test short/long term (1 hr–24 hr) visual learning and memory based on animal bias to explore new objects [42];
3. Open field test for anxiety disorders to test exploratory activity in an environment [43];
4. Morris water maze or Barnes maze tests for spatial and visual learning and memory with averse motivation to assess hippocampal damage [44];
5. Elevated plus maze test for anxiety related responses [43];
6. Passive avoidance test for either short or long term memory of aversive stimulus [45];
7. Y maze test [46] to evaluate spontaneous alternation ability of animals.

VaD animal models

Driven mainly by the fact that there are no existing FDA approved treatment options for VaD, several research studies have aimed at developing a good VaD animal model as a first step to explore treatment options. An ideal animal model should mimic the disease conditions and outcomes as close as possible to human findings. While designing or choosing a VaD model, one should be aware that VaD can be the outcome of several pathophysiological conditions and risk factors either as stand-alone causes or in combination with each other. The common ground for most existing models is the end loss in cognitive abilities.

VaD is associated with the occurrence of a cerebrovascular incident which could be a major stroke in a region capable of compromising cognition like thalamus, frontal lobe or temporal lobe; or could result from a series of several small thromboembolic strokes often silent i.e. without clinical manifestations but accompanied with vessel damage. The most common cause of VaD is SVD (Small Vessel Disease). SVD can induce several isolated lacunar infarcts and ischemic WM lesions. In multiple infarct dementias, thromboembolic events give rise to several microinfarcts in the brain. The underlying molecular pathology in VaD is not clearly understood. Table 2 highlights the characteristics, pathophysiology and limitations of the various animal models discussed below.

1. Vessel Occlusion models

1-1) The 2 vessel occlusion (2VO) or BCCAo (Bilateral CCA occlusion) VaD animal model—The 2VO aimed to model global chronic cerebral hypoperfusion which occurs in human aging and dementia and essentially comprises the permanent occlusion of the bilateral (right and left) common carotid arteries (CCA) [47]. The pathophysiological changes in this model include WM rarefaction, WM damage, BBB disruption (mostly in WM and temporary with maximum permeability at 3 days after BCCAo), neuronal damage in the cortex and hippocampus, infarctions in the striatum of varying sizes confirmed by MRI studies, elevated inflammatory responses and gliosis primarily in the WM [47–50]. Since cognitive impairment is central in dementia, several functional testing results of 2VO rats are available and have reported a higher error rate in the 8-arm radial maze test suggesting learning impairment, deficits and longer latency in the Morris water maze test, poor performance in the elevated T maze test, Y maze and object recognition test [47, 51–54].

The limitations of 2VO model include: this model is restricted to rats since they have a complete circle of Willis, and is not suitable for use in mouse since they lack fully developed posterior communicating arteries of the circle of Willis and can suffer from severe ischemia [55]. In rats, since the degree of ischemia and lesions may vary largely, it is important to carefully outline inclusion criteria based on lesion volume for studying VaD [48]. However, some researchers have used the mouse 2VO model for studying transient global cerebral ischemia, and have found cognitive loss such as anxiety, and decreased spatial memory as well WM lesions, associated gliosis and MMP activation [56, 57]. Another limiting issue involves the sudden and rapid drop in cerebral blood flow post 2VO. To circumvent this issue a recent study has proposed the use of an ameroid (Research

Instruments NW, Lebanon, OR, USA) constrictor device to gradually decrease CBF in their 2 vessel gradual occlusion (2VGO) model [58]. The 2VGO study reported selective WM injury and associated significant loss in spatial memory indicated by the Y maze test. Another effect of the 2VO is retinal and optic nerve damage, and since several cognitive tests require visual learning it is important to verify results with multiple tests [59, 60]. In addition, the 2VO model in Wistar rats from different vendors also induces a notable variability in hippocampal damage, as well as differing post stroke depression among rat strains [61, 62].

1-2) 4VO model—In the 4VO model, both the vertebral arteries (VA) and both the CCAs are occluded on consecutive days [63]. The two VA's are permanently occluded and several modifications of the model have evolved mostly adjusting the duration of CCA occlusion ranging from 15 minutes to permanent occlusion [63, 64]. Occlusion of the vertebral arteries is best achieved by electrocauterization [65]. Various sequences of permanent vessel occlusion have been used. One report indicated a higher mortality with a 2 stage occlusion (2 CCA's followed by 2 VA's) in comparison to a 3 stage occlusion (2 VA's followed by one CCA then another CCA) [64]. The 3 stage 4VO also induced significant cognitive impairment tested by the aversive radial arm functional test [64]. The pathophysiological changes associated with the 4VO model include ischemic neuronal damage and low seizure incidence [63] in middle aged rats, and hippocampal and cortical neuronal damage was observed and cognitive impairment was indicated by radial maze test [66, 67], and poor spatial learning and memory indicated by water maze test [68]. Early neurodegeneration in the hippocampus and cortex identified by Fluoro-Jade and GFAP (Glial fibrillary acidic protein) expression has been reported as early as 24 hours after 4VO that increased progressively up to 72 hours; along with progressively increased immunoreactivity identified by tau expression up to 72 hours after 4VO [69].

There are several limitations to the 4VO model as well. Firstly, the surgery is performed in 2 steps and is at least a 2 day procedure. Secondly, methodological differences in the order of vessel occlusion exist. Thirdly, different occlusion periods of CCA ranging from 10 minutes to permanent occlusion have been reported in literature [63, 64]. Functional outcome is dependent on the occlusion duration. Strain and vendor based discrepancies have also been noted in the 4VO model by the developers of this model [65], maybe in part due to differences in collateral blood supply. These variabilities pose a big setback when comparing results of different studies.

1-3) Unilateral CCA Occlusion (UCCAO) animal model—In this model, one of the CCA's is permanently ligated using a suture [70]. Mice subjected to UCCAO suffered from chronic cerebral hypoperfusion, delayed WM damage in the corpus callosum [70], inflammatory responses such as elevated proinflammatory cytokines and decreased anti-inflammatory cytokines [70], decreased synaptic plasticity [71] and mild neurodegeneration [71]. While, no significant loss was observed in learning and spatial memory; spontaneous alternation; spontaneous motor activity in UCCAO mice, significantly increased anxiety (but not depression) and decreased exploration was observed from the open field and elevated plus maze tests, and short term memory impairment was observed using the novel object

memory test [70, 71]. A disadvantage of this model is that histological infarcts are not readily detectable.

1-4) Bilateral CCA stenosis (BCAS) model—The bilateral CCA's are consecutively occluded by placing micro-coils around the CCA with a 30 min interval between left and right CCA occlusions [72]. It is crucial to carefully select the inner core diameter of the micro-coil as this determines the extent of cerebral damage. WM lesions in the corpus callosum were observed starting at 3 to 7 days after BCAS in rats and after 14 days in mice [72]. This delay has been attributed to a milder CBF reduction in mice compared to rats. In mice, CBF reduction recovered from about 60–70% at 2 hours after BCAS to greater than 80% by 1–3 months [73]. A decrease in brain metabolism (^{18}F-FDG uptake) has been reported with glucose uptake reduced in the cerebral cortex and striatum (at 2hrs 70% and at 2months 88% of pre-BCAS values) and hippocampus (6months: 20% reduction) [73]. BCAS in mice also induces delayed hippocampal atrophy [73], induces inflammatory responses such as MMP activations, gliosis and BBB disruption [74]. Cognitive dysfunction in mice was observed even at 5–6 months after BCAS with deficits in working and reference memory evaluated using radial arm and Barnes maze; and motor deficits observed till 3 months using a beam test and gait analysis; however no reference memory deficits were observed at 30 days after BCAS and spatial memory loss has not been reported [73, 75]. The cognitive dysfunction correlates to the observed WM damage observed starting at 14 days in mice and 3–7 days in rats which may be responsible for the loss in working memory and delayed hippocampal damage at 5–6 months may cause the delayed loss in reference memory [76].

Variations in this model mainly center on the choice of coil diameter which may influence mortality and degree of brain damage. In mice, the use of 0.16mm coil escalated the mortality rates to about 75% versus approximately 10–20%, when using coils of core 0.22mm, 0.20mm, 0.18mm, respectively [72]. This might be due to the greater CBF reduction with decreasing coil diameter. In mice, the 0.18mm micro-coil has been recommended with a promise of high reproducibility [72]. While in rats damage to the visual pathway may occur and interfere with cognitive evaluation [60], when using mice, little to no damage was observed in the gray matter and visual pathway due to a milder CBF decrease and some residual blood flow within the CCAs and its branches [72]. Lastly, the coils have to be procured from a company (like Sawane Spring Co., Ltd., Hamamatsu, Japan) and are typically not reusable which could compound costs when using large animal numbers. Additionally, accumulation of amyloid beta which is typical in AD had been reported after BCAS in mice [77]. The BCAS model does not reflect SVD pathology, instead the occlusion of both CCA's induces chronic hypoperfusion and affects micro vascular flow to induce VaD [77].

2. Multiple infarct and thromboembolism models

In a study involving 425 subjects subjected to dementia evaluation and brain autopsy post death, cortical and sub cortical microinfarcts were found in about 30% of subjects [78]. Microinfarcts increased the probability of dementia, in particular, multiple cortical microinfarcts were a significant risk factor. Microinfarcts were associated with cognitive

decline particularly perceptual speed, semantic and episodic memory [78]. Therefore, the multiple infarction VaD model may be a clinically relevant model. Multiple infarction animal models can be induced by thromboemboli, cholesterol crystals, microbeads or micro-spheres.

2-1) Thromboembolic multiple infarction VaD model—Cerebral emboli and its association with the progression of VaD and AD were recently studied in humans [79]. 60 VaD patients were observed for spontaneous cerebral emboli entering the middle cerebral artery (MCA)'s and decline in cognitive abilities over a period of 2 years using trans-cranial Doppler ultrasound every 6 months. In 45% VaD patients, spontaneous cerebral emboli were positively identified and associated with greater cognitive decline. Studies have shown that a thromboembolic model in rats can cause significant hippocampal injury and cognitive impairment [80] with the size of emboli playing a critical role in determining the extent of neurological deficits and hippocampal injury [80]. When emboli of diameter 48–74μm was employed, at 60 days post embolization significant hippocampal damage in the CA1, 2, 3 regions and poor performance in the water maze test was observed [80].

2-2) Micro-spheres induced multiple infarction VaD model—Multiple infarcts can be induced in the rat brain's cortex, striatum and hippocampus, by injecting about 700–900 micro-spheres of 48–50μm diameter into the right internal carotid artery (ICA) [81, 82]. Sustained decrease in CBF, neuronal damage and impaired energy and neurotransmitter metabolisms were observed in the ischemic side of the brain. These ischemic damages resulted in cognitive impairment. Long escape latency was observed in the water maze test about a week after intravascular embolization, suggesting spatial learning impairment and poor performance in the active and passive avoidance [83, 84]. Cerebral embolization as a model for VaD has been advocated also due to its induction of learning impairments in 3 tasks including one trial active and passive avoidance task as well as two-way active avoidance response in a shuttle box, and the water filled multiple T-maze task [85]. However, the deficits lasted only a few weeks and were not long term cognitive deficits.

2-3) Cholesterol crystals induced multiple infarction VaD model—Another model used cholesterol crystals sized 60–100μm injected into the ICA to induce multiple microinfarcts in the brain, and induces cognitive loss [86]. Both young adult and middle-aged rats were subjected to either a single injection or repeated, bilateral injections given 2 weeks apart. Cognitive testing included open field, motor learning, and Barnes Maze tests. Activation of matrix metalloproteinase (MMPs), microglia and astrocytes indicative of inflammation was observed mainly in the striatum and hippocampus [86]. Middle aged rats after bilateral multiple injections showed cognitive dysfunction but not after single injections [86]. Microembolization using cholesterol crystals can hence induce inflammation and minimal neuronal injury leading to cognitive dysfunction in older animals.

A similar micro infarct model using cholesterol crystals has been studied in mice [87]. A single injection of 40–70μm cholesterol crystals into the ICA produced multiple microinfarcts in the deep cortex, subcortical tissue, and hippocampus. These microinfarcts were associated with microglial and macrophage activation in its core as well reactive astrogliosis in its surrounding. Neuronal injury and death was progressive and increased

with time over a period of 28d after stroke [87]. Delayed demyelination starting at 28d and long lasting gliosis were present. Cognitive decline was measured using the novel object recognition test and hippocampal learning impairment was evident from contextual and tonal fear conditioning tests. The cognitive deficits observed at 7 and 14 days post micro-infarct were not observed at 28 days [87].

Comparison of three multiple infarction VaD models

Rapp et al. also compared infarcts caused by embolism with microthrombi and cholesterol crystals [88]. While thrombus fragments induced discreet infarcts of about 0.1– 1.7mm diameter, cholesterol crystals induced smaller infarcts specifically in the subcortical tissue. With thrombus fragments, the sites of astrocytic and microglial activation overlapped infarcts; using cholesterol crystals, BBB damage and microglial activation were widespread in the brain. These data clearly point out that the extent of brain damage; type of infarcts and associated inflammatory responses depend on the type and size of emboli used. To verify the association of microinfarcts with cognitive decline, a study employed controlled optical methods namely the 2 photon microscopy and occluded individual penetrating vessels on the cortical surface in rat brain [89]. They found that the occlusion of even a single penetrating vessel can lead to microinfarcts and cognitive impairment. In addition, multiple vessel occlusions resulted in coalesced cortical tissue damage, i.e. microinfarcts combining to become large cysts, despite the presence of unobstructed intervening penetrating vessels. This is an important finding of clinical relevance, that not only do microinfarcts lead to cognitive decline but multiple microinfarcts can coalesce and potentially have increased or additive adverse effects [89].

3. High fat diet induced VaD models

There is ample evidence suggesting a strong link between high fat diet (HFD) and cognitive deficits in hippocampus based tasks especially associated with the older population. However, the mechanisms and implications are yet to be fully understood. Rats fed a HFD for 3 months performed poorly in learning and memory tasks, and the extent of cognitive loss was found to be comparable to standard chow fed rats that were aged or had suffered brain damage [90]. The Rotterdam study [91] that investigates occurrences and contributing factors of various neurological diseases among elderly persons had reported that a HFD was associated with cardiovascular risks and dementia. They indicated that in people aged >55 years, intake of high total fat, saturated fat and cholesterol was related to high risks of dementia particularly vascular dementia. A study that fed rats a diet high in saturated fat and sugar reported cognitive deficits in hippocampal-dependent learning and memory processes and also indicated that loss of cognition may precede obesity [92]. However, another report from the Rotterdam study raised a question on the association of HFD with dementia risk [93] and concluded that a diet consisting of high fat (total, saturated, trans fat, cholesterol) was not associated with an increased risk of dementia or its subtype. Some studies have indicated that cognitive impairment and HFD induced oxidative damage was found only when 60% lard based HFD was used, but not with a typical Western diet of 40% HFD [94, 95].

4. Models using risk factors to induce VaD

4-1) Spontaneously hypertensive rats stroke prone (SHRSP)—Hypertension and its association with stroke and dementia have been discussed under risk factors. SHR and SHRSP are the most popular rat strain used in hypertension investigation. While SHRSP rats and their control Wistar-Kyoto (WKY) rats have similar blood supply patterns to the brain, SHRSP rats (normotensive at birth) develop high arterial BP as they age (from 4 weeks to 30 weeks) to about 220mmHG (by 12 weeks) and spontaneously develop ischemic lesions primarily in the cortex (~80%) and secondarily in the basal ganglia [96].

When compared to WKY rats, SHRSP rats had poor learning and memory during their pre stroke phase with worse outcomes post stroke [97]. SHRSP rats after stroke or when subjected to vessel occlusion models (such as UCCAO), with or without salt supplement demonstrate cognitive impairment and develop WM rarefaction and myelin damage, WM lesions with reactive gliosis, small vessel wall hardening, BBB disruption and inflammatory responses were observed [98–101]. Endothelial injury has been implicated to cause blood vessel damage and rupture leading to BBB disruption and micro bleeds [102, 103]. In the hippocampus of SHRSP rats, by 4 months a decrease in white matter and by 6 months a decrease in grey matter in the CA1 and dentate gyrus along with astrogliosis in the CA1 region was observed [104]. In addition to the SHRSP, a model using middle aged SHR rats has been suggested as an early cerebral SVD model [105]; however further studies are required to understand if similar pathology as SHRSP ensues in SHR rats.

One important variation when using SHRSP rats is that they routinely suffer from stroke-like neurological deficits which range from mild to severe paralysis or even death depending on the size of ischemic lesion. Careful selection of animals factoring in motor deficits/ paralysis is needed. Also, neurological deficits and body weight have to be evaluated throughout the study on a regular basis. Visual lesions have been detected by MRI in aged female SHRSP rats and animals show mild in-coordination [101]. Typically, when using models with multiple coexisting or cause-effect conditions (here, hypertension and stroke), analyzing individual effects is difficult and the effects of treatment for one may interfere with results of other. It is relevant to evaluate the effects of hypertension treatment on dementia, and several efforts in this regard have been discussed earlier in the risk factors-hypertension section of this article.

4-2) Diabetic mouse models—Both type one and two diabetes mellitus (T1DM, T2DM) as a risk factor for VaD have been discussed earlier in this article. Briefly, high dose or multiple low doses of Streptozotocin is used for T1DM induction and several obese (readily available, HFD induced) and some non obese mice and rats (GK rats, etc) are used to model T2DM [106]. In STZ induced diabetes, long term cognition has been shown to be affected by diabetes induced alterations to the microvasculature and BBB disruption [107]. In the hippocampus, genes associated with neurogenesis and synaptic plasticity were found to be decreased in T1DM mice [108]. Additionally the inflammatory TL4 (Toll-like receptor 4) signaling pathway and oxidative stress have been implicated in T1DM cognitive decline such as poor learning, memory and anxiety [109, 110]. Upon recurrent or moderate hypoglycemia in T1DM rats, hippocampal microglial activation, decreased dendritic density

and oxidative stress have been associated with cognitive deficits evaluated with Barnes maze and open field tests [111]. In T2DM induction, HFD is often employed, and the effects of HFD on cognition have been discussed earlier in this article. Cognitive loss has also been reported in other T2DM models as well and associated with BBB dysfunction, inflammatory responses and affected neuronal plasticity and neurovascular coupling [112, 113].

In diabetic animal models while cognitive dysfunction has been well established, it should be noted that both VaD and AD or even mixed dementia like symptoms have been reported and careful assessment of amyloid beta pathology, vascular and white matter changes as well as cognitive evaluations are required when choosing animal models to study VaD [114, 115]. Studies on the beneficial effects of diabetes treatments on VaD are warranted.

4-3) Age—Age is a major risk factor for dementia. Age related cognitive decline that worsens with increasing age has been reported by several studies in both mice and rats [116, 117]. It may be important to factor in age, and study aged animals in VaD animal models. However, some of the difficulties involved in studying aged animals include mortality, severe neurological deficits after stroke, occurrence of tumors, and the resulting requirement of using increased animal number to be conclusive of results [118–120].

Pathophysiology and molecular mechanisms of VaD

It is important to understand the pathophysiology of the disease before establishing a good animal model to test treatments. The pathology and mechanisms underlying VaD are yet to be fully understood. It must be noted that the clinical signs and symptoms of VaD may vary depending on the cause and type of VaD and site and size of infarction/damage. Hence, a consensus on defined symptoms and diagnostic procedure has not yet been reached, and routinely neuropsychological and behavioral profiles along with cognitive testing are carried out.

In VaD, chronic hypoperfusion and thromboembolic events, lead to a decrease in CBF, hypoxia, oxidative stress and trigger inflammatory responses. The periventricular WM, basal ganglia, and hippocampus are highly susceptible to hypoperfusion induced lesions. Disruption of the prefrontal-basal ganglia circuitry induces cognitive deficits which is typical in VaD (summarized in Figure 3).

Hypoxia induced oxidative stress leads to mitochondrial dysfunction (and vice versa), neuronal damage and apoptosis via nitric oxide synthase (NOS) pathway, malondialdehyde content, release of reactive oxygen species and free radicals [121–125]. Oxidative stress imbalances the ratio of antioxidants and reactive oxygen species resulting in damage to vessel endothelia, glial and neuronal cells, resulting in neurovascular uncoupling and further CBF reduction [126]. The excess reactive oxygen species can disrupt mitochondrial function and further induce hypoxia and oxidative stress [123]. Cerebral hypoxia can lead to cell death and microvascular dysfunction marked with an increase in vascular inflammatory factors as well as trigger endothelial dysfunction, vascular and BBB leakage, and increases neuro-inflammatory response [127].

Inflammatory factors such as Matrix Metalloproteinase's (MMPs) and microvascular dysfunction degrade the BBB [128, 129] and increase BBB permeability to infiltration of inflammatory factors like interleukins (IL-1, IL-6), MMPs (MMP 2,9), TNFα (Tumor necrosis factor), TLR4 (toll-like receptor 4), C-reactive protein [130] [131]. Upon entry into the brain, these inflammatory factors exacerbate WM damage (demyelination, axonal loss, oligodendrocyte degeneration), cause neuro-degeneration and cell death as well as enhance neuroglial inflammation [132]. Glial secretion of inflammatory factors can exacerbate WM lesions and demyelination by damaging oligodendrocytes [133]. Cerebral WM is highly susceptible to hypoxia induced damage owing to its limited blood supply and poor collateral blood flow in deep structures [134]. In VaD, WM damage arises primarily from demyelination that is attributed to hypoxia induced oligodendrocyte damage [135]. Oligodendrocyte shrinkage and death as well as damage to oligodendrocyte progenitor cells reduce or hinder remyelination [135]. Demyelination delays neural signal transmission and leads to cognitive loss. The result of the inflammatory cascade in the hippocampus is the impairment of neurogenesis, neuronal progenitor cell proliferation, synaptic plasticity and dendritic spine density [136] [137]. Hippocampus based learning and memory deficits ensue.

The vicious cycle of oxidative stress, endothelial and microvascular dysfunction and inflammation exacerbate cerebral damage. The neurovascular unit, a conceptual model that describes functional interactions and signaling between neurons, capillaries, and glia in the brain [138] is dysregulated largely by the interplay between oxidative stress and inflammation resulting in increased BBB disruption, edema, neurovascular uncoupling, and neuronal damage. There exists a complex molecular interaction between these mechanisms and together they result in the disruption of brain homeostasis and neurovascular unit uncoupling [139]. Endothelial injury and platelet activation result in microvascular damage by either adhesion and vasoconstriction or thrombosis and vascular occlusion [89, 140, 141]. Such damage to the arteries and arterioles that supply the deep WM of brain results in white matter infarctions [142].

A rare VaD subtype called CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is caused by a genetic mutation in the Notch3 gene. Among the genes, apolipoprotein E (apoE) has received special attention. While in AD, carriers of the apoE4 allele account for almost 65–80% of all AD patients and its role as a major risk factor has been well documented, there are several conflicting reports about its role in VaD [143]. The presence of cleaved apoE in the hippocampus of VaD brain has been reported recently [144]. It has been suggested that the harboring of one or both apoE4 alleles might be a VaD risk factor but not as potent as it is for AD [143] While the VaD disease pathology has been studied to a certain extent and various factors leading to cognitive dysfunction identified, there is still wide scope in understanding the pathology and broader picture of disease mechanism. There is also a need to develop markers to clearly differentiate VaD from other forms of dementia like AD.

Treatment options

At present, there is no FDA approved treatment for VaD. Hence, several drugs used for AD or that are known to lower cardiovascular risk factors are being employed or studied. These yield modest benefits and control cognitive impairment associated with mild to moderate VaD. Current treatment strategies are mainly attempting to control the progressive nature of VaD induced cognitive dysfunction. The following is a brief discussion of some of the drugs employed in VaD treatment.

Statins are cholesterol lowering drugs. While Simvastatin (oral, 5mg/Kg for 4 weeks) was found to improve cognition, reduce depression, decrease blood serum triglycerides to normal values and increase the number of pyramidal neurons in HFD fed rats [145], the ROCAS (Regression of Cerebral Artery Stenosis) clinical trial [146] concluded that Simvastatin (20 mg/day, daily for 2 years) might at best delay the progression of cerebral WM lesions in patients who already have severe WM lesions.

The N-methyl-D-aspartate (NMDA) receptor is the predominant molecular device for controlling synaptic plasticity and memory function [147]. Memantine is an NMDA antagonist and is FDA approved for the treatment of AD. In mild to moderate severity VaD patients Memantine (10 mg/day, twice a day for 28 weeks) treatment improved cognition [148]. However, NMDA receptor antagonists are also known to cause cognitive loss and induce hallucinations [149].

Donepezil, an oral drug which acts centrally to reversibly inhibit acetylcholinesterase appears to yield some benefits in AD and VaD. Two large clinical trials have reported that Donepezil (5 or 10mg/day, up to 54 weeks) can easily cross the BBB, is well tolerated in humans and improves cognitive functioning [150, 151]. However, it may cause gastrointestinal side effects [152] and has to be used with caution.

Cell-based therapy, such as transplantation of EPCs (endothelial progenitor cells), BMSCs (bone marrow stromal cells) or HUCBCs (human umbilical cord blood cells) induces secretion of trophic factors, increases angiogenesis, neurogenesis and white matter remodeling after stroke [153–157]; and may also hold promise in attenuating cognitive dysfunction. HUCBC treatment improves cognition and reduces amyloid-β-associated neuropathology in Alzheimer mice [158] and also improves spatial memory in neonatal hypoxia-ischemia [159]. In addition, MSCs modulate longitudinal changes in cortical thickness and reduce cognitive decline in patients with multiple system atrophy [160].

Other therapies: Resveratrol treatment targets dementia by reducing oxidative stress [122], and improves cognition possibly through its anti-inflammation and anti-apoptotic actions [161]. Other treatment strategies for neurodegenerative disorders as well as VaD include, TNF-alpha inhibition that significantly reverses hippocampus-dependent cognitive deficits by attenuating the inflammatory factors expression [162, 163], and treatments targeting adult neurogenesis [164]. Pharmacological strategies that affect the dialog between the brain and peripheral immune system show promise as potential novel treatments for stroke [165] and may also benefit VaD.

Conclusions

This review has focused on VaD, its characteristics, risk factors, currently employed animal models as well as current treatment strategies. The limitations of this review article include, that stroke induced VaD has not been discussed. The clinical VaD testing criteria has only been briefly mentioned, as this has been dwelt upon by others, as indicated. The animal models discussed are limited to rodent models of vascular dementia. Using small animals (mice and rats) have several advantages: cost effectiveness, they can be observed for long periods of time, reproducibility and limited variability between testing groups, ease of behavioral and cognitive testing with readily available testing equipment and analysis software, the availability of transgenic mice enables evaluation of specific mechanisms and pathways, and testing therapeutic targets is cost effective as smaller doses are required due to smaller body mass of animals. In the future, there is a need to adapt a standard set of cognitive evaluation criteria including types and time points of testing, and evaluation must encompass tests to assess learning and memory as well as behavioral deficits, motor deficits, anxiety and depression. Also, cognitive evaluation must not rely on the results of a single learning and memory test; instead cognitive evaluation should incorporate several test results, and assess multiple aspects of cognition to be conclusive of VaD and rule out interference from optic pathways damage or neurological deficits. Such uniformity will enable comparisons of different rodent models to determine the most suitable model for evaluating treatment strategies. Understanding the underlying pathology and mechanism of disease is crucial for developing successful treatments of VaD. It is now possible with the aid of immunohistochemistry as well as imaging techniques to evaluate hippocampal atrophy, ischemic lesions, white matter damage, axonal and synaptic deficits, blood brain barrier integrity, inflammatory responses as well cerebral blood flow and perfusion among other mechanisms. The time course and interplay of these mechanisms in VaD should be clarified in order to develop successful interventions and treatments. While neuro-imaging is an important tool used for clinical diagnosis of dementias, experimental animal models have yet to fully exploit the use of MRI in understanding VaD. The role of microRNAs in VaD and their potential use as biomarkers or as treatment strategies has yet to be well explored, and future studies are warranted.

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References

1. Plassman BL, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007; 29(1–2):125–132. [PubMed: 17975326]
2. Xu W, et al. Mid- and late-life diabetes in relation to the risk of dementia: a population-based twin study. Diabetes. 2009; 58(1):71–77. [PubMed: 18952836]
3. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes. 2002; 51(4):1256–1262. [PubMed: 11916953]

4. Leibson CL, et al. Risk of Dementia among Persons with Diabetes Mellitus: A Population-based Cohort Study. Am J Epidemiol. 1997; 145(4):301–308. [PubMed: 9054233]
5. Kimm H, et al. Mid-life and late-life vascular risk factors and dementia in Korean men and women. Arch Gerontol Geriatr. 2011; 52(3):6.
6. Ott A, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999; 53(9):1937–1942. [PubMed: 10599761]
7. Xu W, et al. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. Diabetes. 2010; 59(11):2928–2935. [PubMed: 20713684]
8. Bruce DG, et al. Predictors of cognitive impairment and dementia in older people with diabetes. Diabetologia. 2008; 51(2):241–248. [PubMed: 18060658]
9. Sonnen JA, et al. Different patterns of cerebral injury in dementia with or without diabetes. Arch Neurol. 2009; 66(3):315–322. [PubMed: 19139294]
10. van Harten B, et al. Brain imaging in patients with diabetes: a systematic review. Diabetes Care. 2006; 29(11):2539–2548. [PubMed: 17065699]
11. Idris I, Thomson GA, Sharma JC. Diabetes mellitus and stroke. Int J Clin Pract. 2006; 60(1):48–56. [PubMed: 16409428]
12. Barrett-Connor E, Khaw K-T. DIABETES MELLITUS: AN INDEPENDENT RISK FACTOR FOR STROKE? Am J Epidemiol. 1988; 128(1):116–123. [PubMed: 3381820]
13. You R, et al. Risk factors for lacunar infarction syndromes. Neurology. 1995; 45(8):1483–1487. [PubMed: 7644045]
14. Weir CJ, et al. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. BMJ. 1997; 314(7090):1303. [PubMed: 9158464]
15. Megherbi SE, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. Stroke. 2003; 34(3):688–694. [PubMed: 12624292]
16. Anderson GH. Effect of age on hypertension: analysis of over 4,800 referred hypertensive patients. Saudi J Kidney Dis Transpl. 1999; 10(3):286–297. [PubMed: 18212439]
17. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and dementia - a comprehensive review. Ther Adv Neurol Disord. 2009; 2(4):241–260. [PubMed: 21179532]
18. Yamada M, et al. Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. J Am Geriatr Soc. 2003; 51(3):410–414. [PubMed: 12588587]
19. Ronnemaa E, et al. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. Dement Geriatr Cogn Disord. 2011; 31(6):460–466. [PubMed: 21791923]
20. Launer LJ, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000; 21(1):49–55. [PubMed: 10794848]
21. Korf ES, et al. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. Hypertension. 2004; 44(1):29–34. [PubMed: 15159381]
22. Verhaaren BF, et al. High blood pressure and cerebral white matter lesion progression in the general population. Hypertension. 2013; 61(6):1354–1359. [PubMed: 23529163]
23. Tzourio C, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med. 2003; 163(9):1069–1075. [PubMed: 12742805]
24. Forette F, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med. 2002; 162(18):2046–2052. [PubMed: 12374512]
25. Farmer ME, et al. Blood pressure and cognitive performance. The Framingham Study. Am J Epidemiol. 1987; 126(6):1103–1114. [PubMed: 3687920]
26. Guo Z, et al. Low blood pressure and dementia in elderly people: the Kungsholmen project. BMJ. 1996; 312(7034):805–808. [PubMed: 8608286]
27. Zhu L, et al. Blood pressure reduction, cardiovascular diseases, and cognitive decline in the mini-mental state examination in a community population of normal very old people: a three-year follow-up. J Clin Epidemiol. 1998; 51(5):385–391. [PubMed: 9619965]

28. Qiu C, et al. Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. Stroke. 2004; 35(8):1810–1815. [PubMed: 15232128]
29. Grundy SM, et al. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation. 2004 Feb 3; 109(4):551–556. [PubMed: 14757684]
30. Frisardi V. Impact of Metabolic Syndrome on Cognitive Decline in Older Age: Protective or Harmful, Where is the Pitfall? J Alzheimers Dis. 2014; 4:4.
31. Siervo M, et al. Metabolic Syndrome and Longitudinal Changes in Cognitive Function: A Systematic Review and Meta-Analysis. J Alzheimers Dis. 2014; 27:27.
32. Rouch I, et al. Metabolic Syndrome is Associated with Poor Memory and Executive Performance in Elderly Community Residents: The PROOF Study. Am J Geriatr Psychiatry. 2014; 25(14): 00032–00033.
33. Liu CL, et al. Late-life metabolic syndrome prevents cognitive decline among older men aged 75 years and over: one-year prospective cohort study. J Nutr Health Aging. 2013; 17(6):523–526. [PubMed: 23732548]
34. Raffaitin C, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. Diabetes Care. 2009; 32(1):169–174. [PubMed: 18945929]
35. Birdsill AC, et al. Low cerebral blood flow is associated with lower memory function in metabolic syndrome. Obesity. 2013; 21(7):1313–1320. [PubMed: 23687103]
36. Solfrizzi V, et al. Metabolic syndrome, mild cognitive impairment, and progression to dementia. The Italian Longitudinal Study on Aging. Neurobiol Aging. 2011; 32(11):1932–1941. [PubMed: 20045217]
37. Solfrizzi V, et al. Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. J Neurol Neurosurg Psychiatry. 2010; 81(4):433–440. [PubMed: 19965842]
38. Yaffe K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004; 292(18):2237–2242. [PubMed: 15536110]
39. Lee AY. Vascular dementia. Chonnam Med J. 2011; 47(2):66–71. [PubMed: 22111063]
40. Wetterling T, Kanitz RD, Borgis KJ. Comparison of different diagnostic criteria for vascular dementia (ADDTC, DSM-IV, ICD-10, NINDS-AIREN). Stroke. 1996; 27(1):30–36. [PubMed: 8553399]
41. Spinetta MJ, et al. Alcohol-induced retrograde memory impairment in rats: prevention by caffeine. Psychopharmacology (Berl). 2008; 201(3):361–371. [PubMed: 18758756]
42. Stuart SA, et al. Chronic pravastatin but not atorvastatin treatment impairs cognitive function in two rodent models of learning and memory. PLoS One. 2013; 8(9):e75467. [PubMed: 24040413]
43. Brown R, Corey S, Moore A. Differences in Measures of Exploration and Fear in MHC-Congenic C57BL/6J and B6-H-2K Mice. Behavior Genetics. 1999; 29(4):263–271.
44. Ohno M, et al. Differential effects of alphaCaMKII mutation on hippocampal learning and changes in intrinsic neuronal excitability. Eur J Neurosci. 2006; 23(8):2235–2240. [PubMed: 16630070]
45. Ishiyama T, et al. Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test. Eur J Pharmacol. 2007; 572(2–3):160–170. [PubMed: 17662268]
46. Weiss C, Shroff A, Disterhoft JF. Spatial learning and memory in aging C57BL/6 mice. Neuroscience Research Communications. 1998; 23(2):77–92.
47. Nanri M, Watanabe H. [Availability of 2VO rats as a model for chronic cerebrovascular disease]. Nihon Yakurigaku Zasshi. 1999; 113(2):85–95. [PubMed: 10205783]
48. Soria G, et al. The ins and outs of the BCCAo model for chronic hypoperfusion: a multimodal and longitudinal MRI approach. PLoS One. 2013; 8(9):e74631. [PubMed: 24058609]
49. Wakita H, et al. Glial activation and white matter changes in the rat brain induced by chronic cerebral hypoperfusion: an immunohistochemical study. Acta Neuropathol. 1994; 87(5):484–492. [PubMed: 8059601]
50. Ueno M, et al. Blood-brain barrier disruption in white matter lesions in a rat model of chronic cerebral hypoperfusion. J Cereb Blood Flow Metab. 2002; 22(1):97–104. [PubMed: 11807399]

51. Sarti C, et al. Persistent impairment of gait performances and working memory after bilateral common carotid artery occlusion in the adult Wistar rat. Behav Brain Res. 2002; 136(1):13–20. [PubMed: 12385786]
52. Lee S, et al. Depressive-Like Behaviors in a Rat Model of Chronic Cerebral Hypoperfusion. Translational Stroke Research. 2014:1–8.
53. Zhang ZH, et al. Comparison of cognitive performance between two rat models of vascular dementia. Int J Neurosci. 2014; 124(11):818–823. [PubMed: 24397495]
54. de Bortoli VC, et al. Inhibitory avoidance memory retention in the elevated T-maze is impaired after perivascular manipulation of the common carotid arteries. Life Sci. 2005; 76(18):2103–2114. [PubMed: 15826877]
55. Farkas E, Luiten PG, Bari F. Permanent, bilateral common carotid artery occlusion in the rat: a model for chronic cerebral hypoperfusion-related neurodegenerative diseases. Brain Res Rev. 2007; 54(1):162–180. [PubMed: 17296232]
56. Walker EJ, Rosenberg GA. Divergent role for MMP-2 in myelin breakdown and oligodendrocyte death following transient global ischemia. J Neurosci Res. 2010; 88(4):764–773. [PubMed: 19830840]
57. Lai M, et al. Forebrain mineralocorticoid receptor overexpression enhances memory, reduces anxiety and attenuates neuronal loss in cerebral ischaemia. European Journal of Neuroscience. 2007; 25(6):1832–1842. [PubMed: 17432969]
58. Kitamura A, et al. Selective white matter abnormalities in a novel rat model of vascular dementia. Neurobiol Aging. 2012; 33(5):1. [PubMed: 20363053]
59. Stevens WD, Fortin T, Pappas BA. Retinal and Optic Nerve Degeneration After Chronic Carotid Ligation: Time Course and Role of Light Exposure. Stroke. 2002; 33(4):1107–1112. [PubMed: 11935068]
60. Yamamoto H, et al. Complex neurodegeneration in retina following moderate ischemia induced by bilateral common carotid artery occlusion in Wistar rats. Exp Eye Res. 2006; 82(5):767–779. [PubMed: 16359664]
61. Marosi M, et al. Hippocampal (CA1) activities in Wistar rats from different vendors. Fundamental differences in acute ischemia. J Neurosci Methods. 2006; 156(1–2):231–235. [PubMed: 16621009]
62. Kunze A, et al. Strain differences in fatigue and depression after experimental stroke. Transl Stroke Res. 2014; 5(5):604–611. [PubMed: 24916273]
63. Pulsinelli WA, Brierley JB. A new model of bilateral hemispheric ischemia in the unanesthetized rat. Stroke. 1979; 10(3):267–272. [PubMed: 37614]
64. Neto CJ, et al. Permanent, 3-stage, 4-vessel occlusion as a model of chronic and progressive brain hypoperfusion in rats: a neurohistological and behavioral analysis. Behav Brain Res. 2005; 160(2): 312–322. [PubMed: 15863227]
65. Pulsinelli WA, Buchan AM. The four-vessel occlusion rat model: method for complete occlusion of vertebral arteries and control of collateral circulation. Stroke. 1988; 19(7):913–914. [PubMed: 3291205]
66. Ferreira ED, et al. Middle-aged, but not young, rats develop cognitive impairment and cortical neurodegeneration following the four-vessel occlusion/internal carotid artery model of chronic cerebral hypoperfusion. Eur J Neurosci. 2011; 34(7):1131–1140. [PubMed: 21884555]
67. Dias Fiuza Ferreira E, et al. Sildenafil provides sustained neuroprotection in the absence of learning recovery following the 4-vessel occlusion/internal carotid artery model of chronic cerebral hypoperfusion in middle-aged rats. Brain Res Bull. 2013; 90:58–65. [PubMed: 22982173]
68. Kim YO, et al. Effects of sinapic Acid of 4 vessel occlusion model-induced ischemia and cognitive impairments in the rat. Clin Psychopharmacol Neurosci. 2011; 9(2):86–90. [PubMed: 23429437]
69. Cespedes AE, Arango CA, Cardona GP. [Injury markers in two models of cerebral ischemia]. Biomedica. 2013; 33(2):292–305. [PubMed: 24652140]
70. Yoshizaki K, et al. Chronic cerebral hypoperfusion induced by right unilateral common carotid artery occlusion causes delayed white matter lesions and cognitive impairment in adult mice. Exp Neurol. 2008; 210(2):585–591. [PubMed: 18222425]

71. Zhao Y, et al. Chronic cerebral hypoperfusion causes decrease of O-GlcNAcylation, hyperphosphorylation of tau and behavioral deficits in mice. Front Aging Neurosci. 2014; 6:10. [PubMed: 24575038]
72. Shibata M, et al. White matter lesions and glial activation in a novel mouse model of chronic cerebral hypoperfusion. Stroke. 2004; 35(11):2598–2603. [PubMed: 15472111]
73. Nishio K, et al. A mouse model characterizing features of vascular dementia with hippocampal atrophy. Stroke. 2010; 41(6):1278–1284. [PubMed: 20448204]
74. Nakaji K, et al. Matrix metalloproteinase-2 plays a critical role in the pathogenesis of white matter lesions after chronic cerebral hypoperfusion in rodents. Stroke. 2006; 37(11):2816–2823. [PubMed: 17008622]
75. Shibata M, et al. Selective impairment of working memory in a mouse model of chronic cerebral hypoperfusion. Stroke. 2007; 38(10):2826–2832. [PubMed: 17761909]
76. Ihara M, Tomimoto H. Lessons from a Mouse Model Characterizing Features of Vascular Cognitive Impairment with White Matter Changes. Journal of Aging Research. 2011:2011.
77. Khan M, et al. Remote Ischemic Postconditioning: Harnessing Endogenous Protection in a Murine Model of Vascular Cognitive Impairment. Translational Stroke Research. 2015; 6(1):69–77. [PubMed: 25351177]
78. Arvanitakis Z, et al. Microinfarct pathology, dementia, and cognitive systems. Stroke. 2011; 42(3): 722–727. [PubMed: 21212395]
79. Purandare N, et al. Association of cerebral emboli with accelerated cognitive deterioration in Alzheimer's disease and vascular dementia. Am J Psychiatry. 2012; 169(3):300–308. [PubMed: 22193532]
80. Zhang HA, et al. Evaluation of hippocampal injury and cognitive function induced by embolization in the rat brain. Anat Rec. 2013; 296(8):1207–1214.
81. Takagi K, Takeo S. [The model of stroke induced by microsphere embolism in rats]. Nihon Yakurigaku Zasshi. 2003; 121(6):440–446. [PubMed: 12835538]
82. Miyake K, Takeo S, Kaijihara H. Sustained decrease in brain regional blood flow after microsphere embolism in rats. Stroke. 1993; 24(3):415–420. [PubMed: 8446979]
83. Fukatsu T, et al. Effects of nefiracetam on spatial memory function and acetylcholine and GABA metabolism in microsphere-embolized rats. Eur J Pharmacol. 2002; 453(1):59–67. [PubMed: 12393060]
84. Takagi N, et al. Failure in learning task and loss of cortical cholingergic fibers in microsphere-embolized rats. Exp Brain Res. 1997; 114(2):279–287. [PubMed: 9166917]
85. Kiyota Y, et al. Cerebral embolization leads to memory impairment of several learning tasks in rats. Pharmacol Biochem Behav. 1986; 24(3):687–692. [PubMed: 3703902]
86. Rapp JH, et al. Microemboli composed of cholesterol crystals disrupt the blood-brain barrier and reduce cognition. Stroke. 2008; 39(8):2354–2361. [PubMed: 18566307]
87. Wang M, et al. Cognitive deficits and delayed neuronal loss in a mouse model of multiple microinfarcts. J Neurosci. 2012; 32(50):17948–17960. [PubMed: 23238711]
88. Rapp JH, Hollenbeck K, Pan XM. An experimental model of lacunar infarction: embolization of microthrombi. J Vasc Surg. 2008; 48(1):196–200. [PubMed: 18486421]
89. Shih AY, et al. The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit. Nat Neurosci. 2013; 16(1):55–63. [PubMed: 23242312]
90. Winocur G, Greenwood CE. Studies of the effects of high fat diets on cognitive function in a rat model. Neurobiol Aging. 2005; 1:46–49. [PubMed: 16219391]
91. Kalmijn S, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol. 1997; 42(5):776–782. [PubMed: 9392577]
92. Davidson TL, et al. Inter-relationships among diet, obesity and hippocampal-dependent cognitive function. Neuroscience. 2013; 253:110–122. [PubMed: 23999121]
93. Engelhart MJ, et al. Diet and risk of dementia: Does fat matter?: The Rotterdam Study. Neurology. 2002; 59(12):1915–1921. [PubMed: 12499483]
94. Pistell PJ, et al. Cognitive impairment following high fat diet consumption is associated with brain inflammation. J Neuroimmunol. 2010; 219(1–2):25–32. [PubMed: 20004026]

95. Morrison CD, et al. High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. J Neurochem. 2010; 114(6):1581–1589. [PubMed: 20557430]

96. Yamori Y, et al. Pathogenetic similarity of strokes in stroke-prone spontaneously hypertensive rats and humans. Stroke. 1976; 7(1):46–53. [PubMed: 1258104]

97. Yamaguchi M, et al. Memory deficit accompanying cerebral neurodegeneration after stroke in stroke-prone spontaneously hypertensive rats (SHRSP). Acta Neurochir Suppl. 1994; 60:200–202. [PubMed: 7976546]

98. Jalal FY, et al. Myelin loss associated with neuroinflammation in hypertensive rats. Stroke. 2012; 43(4):1115–1122. [PubMed: 22363061]

99. Fredriksson K, et al. Cerebrovascular lesions in stroke-prone spontaneously hypertensive rats. Acta Neuropathol. 1985; 68(4):284–294. [PubMed: 4090940]

100. Chiba T, et al. Interleukin-1beta accelerates the onset of stroke in stroke-prone spontaneously hypertensive rats. Mediators Inflamm. 2012; 2012:701976. [PubMed: 23326018]

101. Henning EC, Warach S, Spatz M. Hypertension-induced vascular remodeling contributes to reduced cerebral perfusion and the development of spontaneous stroke in aged SHRSP rats. J Cereb Blood Flow Metab. 2010; 30(4):827–8236. [PubMed: 19953101]

102. Schreiber S, et al. Blood brain barrier breakdown as the starting point of cerebral small vessel disease? - New insights from a rat model. Exp Transl Stroke Med. 2013; 5(1):4. [PubMed: 23497521]

103. Li H, et al. Evaluation of the protective potential of brain microvascular endothelial cell autophagy on blood-brain barrier integrity during experimental cerebral ischemia-reperfusion injury. Transl Stroke Res. 2014; 5(5):618–626. [PubMed: 25070048]

104. Sabbatini M, et al. The hippocampus in spontaneously hypertensive rats: an animal model of vascular dementia? Mech Ageing Dev. 2002; 123(5):547–559. [PubMed: 11796140]

105. Kaiser D, et al. Spontaneous white matter damage, cognitive decline and neuroinflammation in middle-aged hypertensive rats: an animal model of early-stage cerebral small vessel disease. Acta Neuropathol Commun. 2014; 2(1):169. [PubMed: 25519173]

106. King AJ. The use of animal models in diabetes research. Br J Pharmacol. 2012; 166(3):877–894. [PubMed: 22352879]

107. Huber JD, VanGilder RL, Houser KA. Streptozotocin-induced diabetes progressively increases blood-brain barrier permeability in specific brain regions in rats. Am J Physiol Heart Circ Physiol. 2006; 291(6):H2660–H2668. [PubMed: 16951046]

108. Thomas J, Garg ML, Smith DW. Dietary resveratrol supplementation normalizes gene expression in the hippocampus of streptozotocin-induced diabetic C57Bl/6 mice. J Nutr Biochem. 2014; 25(3):313–318. [PubMed: 24456733]

109. Kawamoto EM, et al. TLR4-dependent metabolic changes are associated with cognitive impairment in an animal model of type 1 diabetes. Biochem Biophys Res Commun. 2014; 443(2):731–737. [PubMed: 24342620]

110. Alvarez EO, et al. Cognitive dysfunction and hippocampal changes in experimental type 1 diabetes. Behav Brain Res. 2009; 198(1):224–230. [PubMed: 19041902]

111. Won SJ, et al. Recurrent/moderate hypoglycemia induces hippocampal dendritic injury, microglial activation, and cognitive impairment in diabetic rats. J Neuroinflammation. 2012; 9:182. [PubMed: 22830525]

112. Tsukuda K, et al. Amelioration of cognitive impairment in the type-2 diabetic mouse by the angiotensin II type-1 receptor blocker candesartan. Hypertension. 2007; 50(6):1099–1105. [PubMed: 17968000]

113. Serlin Y, Levy J, Shalev H. Vascular pathology and blood-brain barrier disruption in cognitive and psychiatric complications of type 2 diabetes mellitus. Cardiovasc Psychiatry Neurol. 2011; 2011:609202. [PubMed: 21350721]

114. Wang JQ, et al. Brain aging and AD-like pathology in streptozotocin-induced diabetic rats. J Diabetes Res. 2014; 2014:796840. [PubMed: 25197672]

115. Li X, Song D, Leng SX. Link between type 2 diabetes and Alzheimer's disease: from epidemiology to mechanism and treatment. Clin Interv Aging. 2015; 10:549–560. [PubMed: 25792818]
116. Goldman H, et al. Cerebrovascular permeability and cognition in the aging rat. Neurobiol Aging. 1992; 13(1):57–62. [PubMed: 1542382]
117. Park L, et al. Nox2-derived reactive oxygen species mediate neurovascular dysregulation in the aging mouse brain. J Cereb Blood Flow Metab. 2007; 27(12):1908–1918. [PubMed: 17429347]
118. Manwani B, et al. Perfusion of ischemic brain in young and aged animals: a laser speckle flowmetry study. Stroke. 2014; 45(2):571–578. [PubMed: 24357659]
119. Lindner MD, et al. Long-lasting functional disabilities in middle-aged rats with small cerebral infarcts. J Neurosci. 2003; 23(34):10913–10922. [PubMed: 14645487]
120. Bruley-Rosset M, et al. Prevention of spontaneous tumors of aged mice by immunopharmacologic manipulation: study of immune antitumor mechanisms. J Natl Cancer Inst. 1981; 66(6):1113–1119. [PubMed: 6972461]
121. Li WZ, et al. Protective effect of bilobalide on learning and memory impairment in rats with vascular dementia. Mol Med Rep. 2013; 8(3):935–941. [PubMed: 23835946]
122. Ma X, et al. Resveratrol improves cognition and reduces oxidative stress in rats with vascular dementia. Neural Regen Res. 2013; 8(22):2050–2059. [PubMed: 25206513]
123. Zhang X, et al. Effects of acupuncture on declined cerebral blood flow, impaired mitochondrial respiratory function and oxidative stress in multi-infarct dementia rats. Neurochem Int. 2014; 65:23–29. [PubMed: 24361538]
124. Huang JL, et al. Protective effects of Nicotiflorin on reducing memory dysfunction, energy metabolism failure and oxidative stress in multi-infarct dementia model rats. Pharmacol Biochem Behav. 2007; 86(4):741–748. [PubMed: 17448528]
125. Ritz MF, et al. Gene expression suggests spontaneously hypertensive rats may have altered metabolism and reduced hypoxic tolerance. Curr Neurovasc Res. 2012; 9(1):10–19. [PubMed: 22272763]
126. Liu H, Zhang J. Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress. Int J Neurosci. 2012; 122(9):494–499. [PubMed: 22519891]
127. Gill R, Tsung A, Billiar T. Linking oxidative stress to inflammation: Toll-like receptors. Free Radic Biol Med. 2010; 48(9):1121–1132. [PubMed: 20083193]
128. Candelario-Jalil E, et al. Matrix metalloproteinases are associated with increased blood-brain barrier opening in vascular cognitive impairment. Stroke. 2011; 42(5):1345–1350. [PubMed: 21454822]
129. Reuter B, et al. Effect of simvastatin on MMPs and TIMPs in human brain endothelial cells and experimental stroke. Transl Stroke Res. 2015; 6(2):156–159. [PubMed: 25476155]
130. Iemolo F, et al. Pathophysiology of vascular dementia. Immun Ageing. 2009; 6:13. [PubMed: 19895675]
131. Li W, Lai XS. [Changes of interleukin-1beta and TNF-alpha contents in the hippocampus and the interventional effect of electroacupuncture in vascular dementia rats]. Zhen Ci Yan Jiu. 2007; 32(1):34–37. [PubMed: 17580438]
132. Chen J, et al. White matter damage and the effect of matrix metalloproteinases in type 2 diabetic mice after stroke. Stroke. 2011; 42(2):445–452. [PubMed: 21193743]
133. Wang J, Zhang HY, Tang XC. Huperzine a improves chronic inflammation and cognitive decline in rats with cerebral hypoperfusion. J Neurosci Res. 2010; 88(4):807–815. [PubMed: 19795377]
134. Back SA, et al. Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. J Neurosci. 2002; 22(2):455–463. [PubMed: 11784790]
135. Ihara M, et al. Quantification of myelin loss in frontal lobe white matter in vascular dementia, Alzheimer's disease, and dementia with Lewy bodies. Acta Neuropathol. 2010; 119(5):579–589. [PubMed: 20091409]
136. Park HR, et al. A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. Neurosci Lett. 2010; 482(3):235–239. [PubMed: 20670674]

137. Stranahan AM, et al. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. Hippocampus. 2008; 18(11):1085–1088. [PubMed: 18651634]
138. Chen J, et al. Neurorestorative therapy for stroke. Front Hum Neurosci. 2014; 8:382. [PubMed: 25018718]
139. Stanimirovic DB, Friedman A. Pathophysiology of the neurovascular unit: disease cause or consequence? J Cereb Blood Flow Metab. 2012; 32(7):1207–1221. [PubMed: 22395208]
140. Barker R, et al. Pathophysiology of white matter perfusion in Alzheimer's disease and vascular dementia. Brain. 2014; 137(Pt 5):1524–1532. [PubMed: 24618270]
141. Song J, et al. Association between risk factors for vascular dementia and adiponectin. Biomed Res Int. 2014; 2014:261672. [PubMed: 24860814]
142. Brun A. Pathology and pathophysiology of cerebrovascular dementia: pure subgroups of obstructive and hypoperfusive etiology. Dementia. 1994; 5(3–4):145–147. [PubMed: 8087169]
143. Rohn TT. Is apolipoprotein E4 an important risk factor for vascular dementia? Int J Clin Exp Pathol. 2014; 7(7):3504–3511. [PubMed: 25120729]
144. Rohn TT, et al. Apolipoprotein E pathology in vascular dementia. Int J Clin Exp Pathol. 2014; 7(3):938–947. [PubMed: 24696712]
145. Can OD, et al. The effect of simvastatin treatment on behavioral parameters, cognitive performance, and hippocampal morphology in rats fed a standard or a high-fat diet. Behav Pharmacol. 2012; 23(5–6):582–592. [PubMed: 22797467]
146. Mok VC, et al. Effects of statins on the progression of cerebral white matter lesion: Post hoc analysis of the ROCAS (Regression of Cerebral Artery Stenosis) study. J Neurol. 2009; 256(5): 750–757. [PubMed: 19252811]
147. Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. Prog Neurobiol. 2014; 115:157–188. [PubMed: 24361499]
148. Orgogozo JM, et al. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke. 2002; 33(7):1834–1839. [PubMed: 12105362]
149. Lipton SA. Failures and successes of NMDA receptor antagonists: molecular basis for the use of open-channel blockers like memantine in the treatment of acute and chronic neurologic insults. NeuroRx. 2004; 1(1):101–110. [PubMed: 15717010]
150. Wilkinson D, et al. Donepezil in vascular dementia: a randomized, placebo-controlled study. Neurology. 2003; 61(4):479–486. [PubMed: 12939421]
151. Wilkinson D, et al. The long-term efficacy and tolerability of donepezil in patients with vascular dementia. Int J Geriatr Psychiatry. 2010; 25(3):305–313. [PubMed: 19623601]
152. Dunn NR, Pearce GL, Shakir SA. Adverse effects associated with the use of donepezil in general practice in England. J Psychopharmacol. 2000; 14(4):406–408. [PubMed: 11198060]
153. Liu J, et al. Vascular remodeling after ischemic stroke: mechanisms and therapeutic potentials. Prog Neurobiol. 2014; 115:138–156. [PubMed: 24291532]
154. Liu X, et al. Cell based therapies for ischemic stroke: from basic science to bedside. Prog Neurobiol. 2014; 115:92–115. [PubMed: 24333397]
155. Yan T, et al. HUCBCs increase angiopoietin 1 and induce neurorestorative effects after stroke in T1DM rats. CNS Neurosci Ther. 2014; 20(10):935–944. [PubMed: 25042092]
156. Chen J, et al. Neurorestorative therapy for stroke. Front Hum Neurosci. 2014; 8(382)
157. Cui X, et al. Therapeutic benefit of treatment of stroke with simvastatin and human umbilical cord blood cells: neurogenesis, synaptic plasticity, and axon growth. Cell Transplant. 2012; 21(5):845–856. [PubMed: 22405262]
158. Darlington D, et al. Multiple low-dose infusions of human umbilical cord blood cells improve cognitive impairments and reduce amyloid-beta-associated neuropathology in Alzheimer mice. Stem Cells Dev. 2013; 22(3):412–421. [PubMed: 22816379]
159. de Paula S, et al. The dose-response effect of acute intravenous transplantation of human umbilical cord blood cells on brain damage and spatial memory deficits in neonatal hypoxia-ischemia. Neuroscience. 2012; 210:431–441. [PubMed: 22441035]

160. Sunwoo MK, et al. Mesenchymal stem cells can modulate longitudinal changes in cortical thickness and its related cognitive decline in patients with multiple system atrophy. Front Aging Neurosci. 2014; 6(118)

161. Li XM, et al. Resveratrol pretreatment attenuates the isoflurane-induced cognitive impairment through its anti-inflammation and -apoptosis actions in aged mice. J Mol Neurosci. 2014; 52(2): 286–293. [PubMed: 24126892]

162. Belarbi K, et al. TNF-alpha protein synthesis inhibitor restores neuronal function and reverses cognitive deficits induced by chronic neuroinflammation. J Neuroinflammation. 2012; 9(23): 1742–2094.

163. Tweedie D, Sambamurti K, Greig NH. TNF-alpha inhibition as a treatment strategy for neurodegenerative disorders: new drug candidates and targets. Curr Alzheimer Res. 2007; 4(4): 378–385. [PubMed: 17908040]

164. Ruan L, et al. Neurogenesis in neurological and psychiatric diseases and brain injury: from bench to bedside. Prog Neurobiol. 2014; 115:116–137. [PubMed: 24384539]

165. An C, et al. Molecular dialogs between the ischemic brain and the peripheral immune system: dualistic roles in injury and repair. Prog Neurobiol. 2014; 115:6–24. [PubMed: 24374228]

Highlights/Outline

- Introduction
  - Define VaD
  - Similarities and differences with AD
- Risk factors of vascular dementia
  - Diabetes
  - Hypertension
  - Metabolic syndrome
- Evaluation of cognitive dysfunction
- VaD animal models
  - Vessel Occlusion models
  - Multiple infarct and Thromboembolism models
  - High fat diet models
  - Models using risk factors to induce dementia
- Pathophysiology and molecular mechanisms of VaD
- Treatment options for VaD

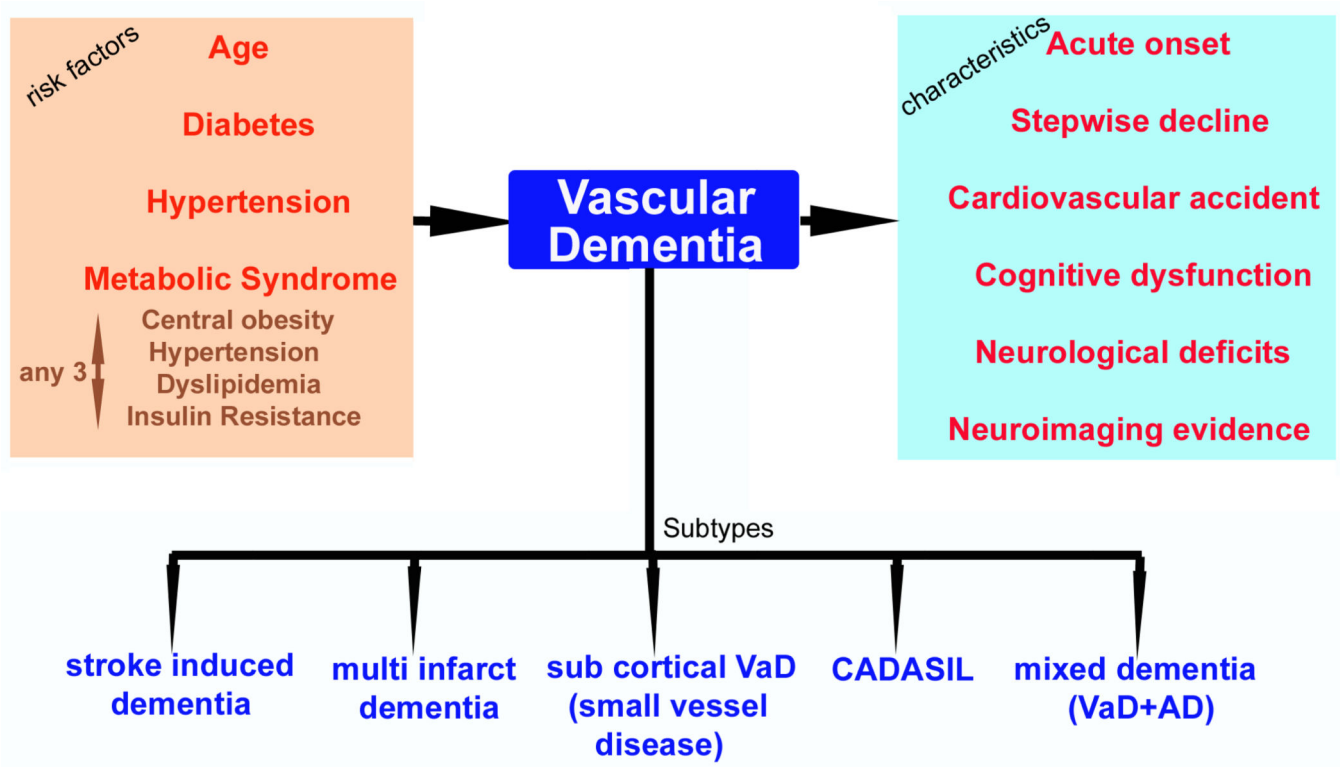

Figure 1.
Summarizes the risk factors, subtypes and characteristic features of VaD.

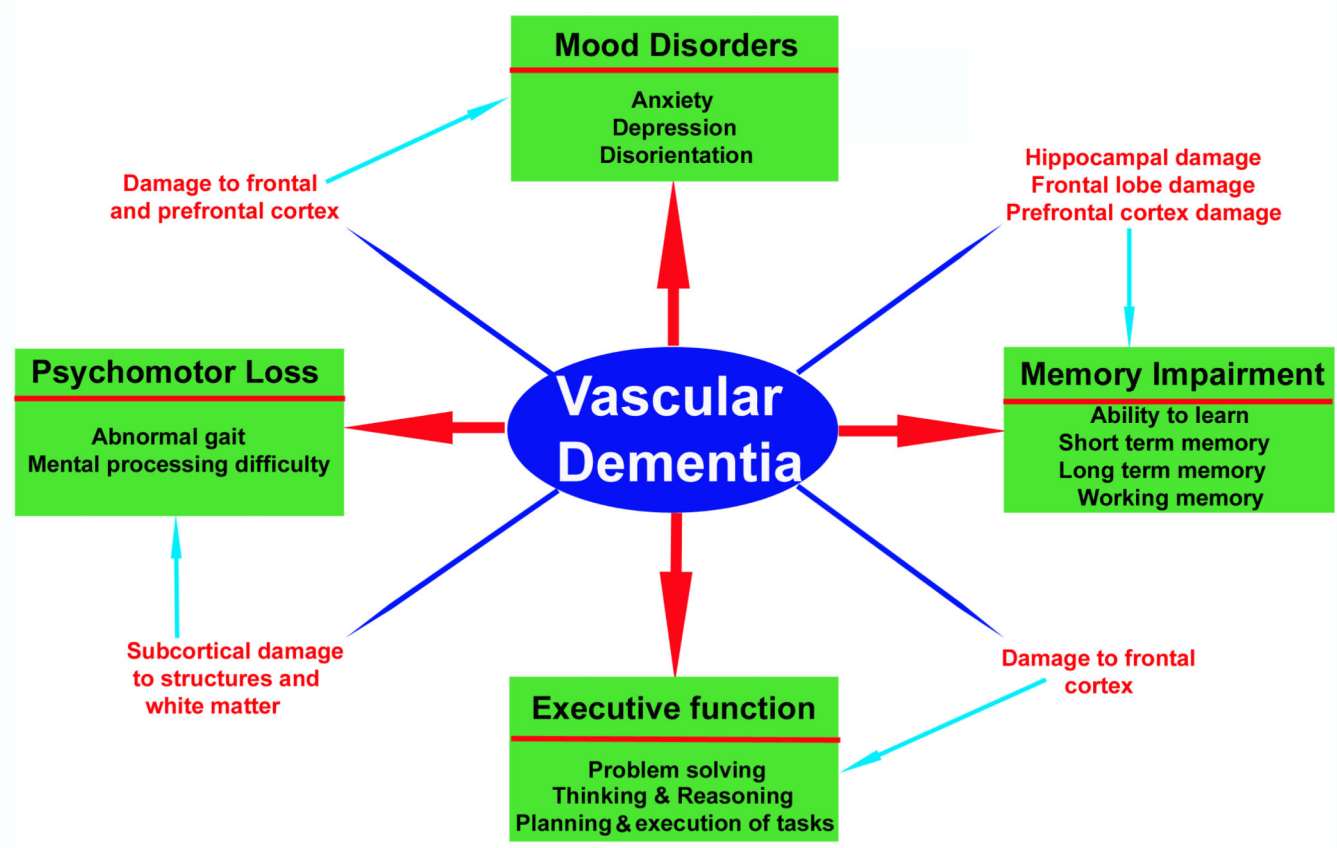

Figure 2.
Summarizes the various cognitive disabilities of VaD patients and associated brain damage.

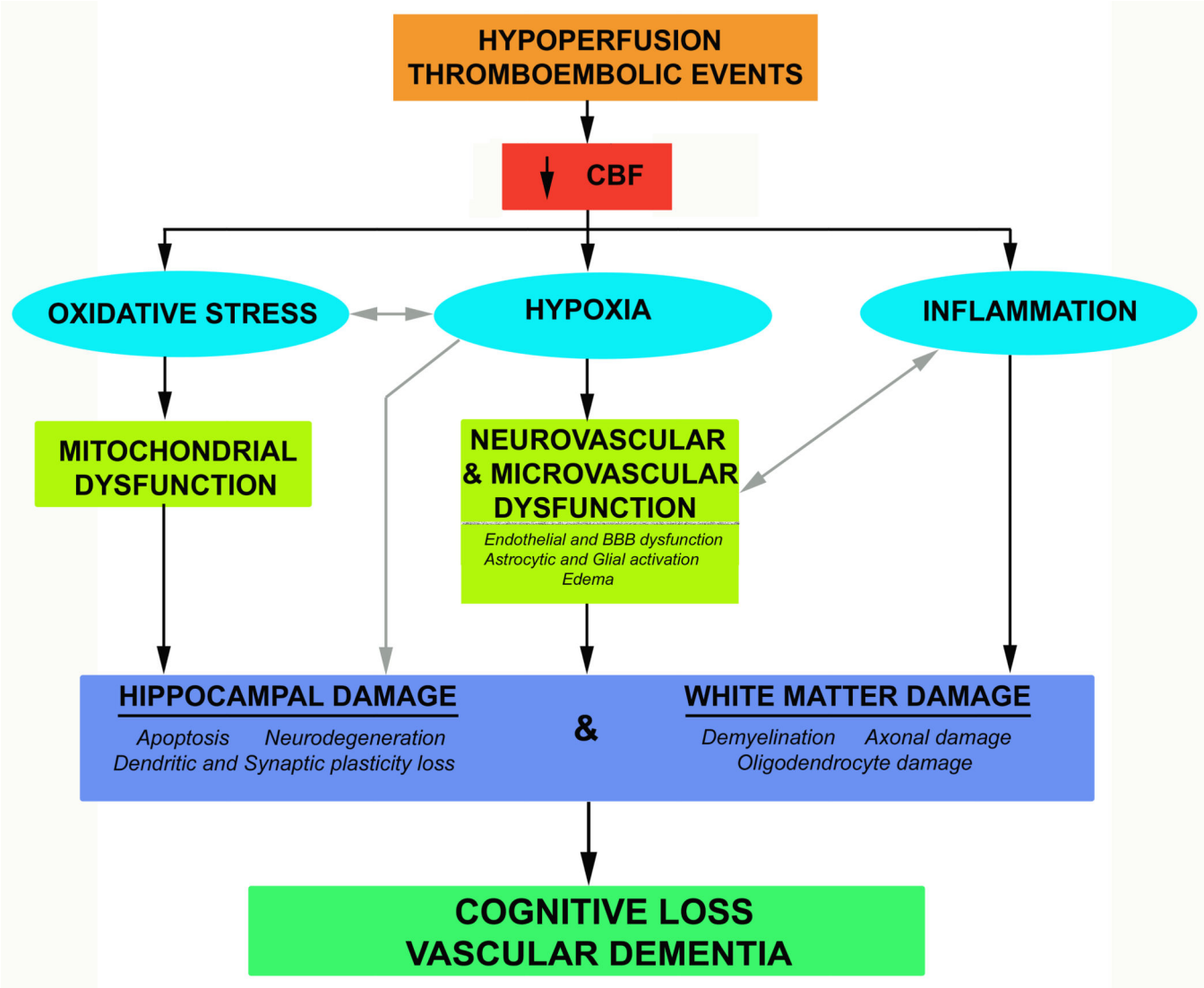

Figure 3.
Summarizes the various mechanism implicated in the pathogenesis of VaD.

Alzheimer's Disease	Vascular Dementia
SYMPTOMS	
➤ Gradual onset ➤ No neurological deficits ➤ Normal Gait ➤ Language related issues during oral or written communication and vocabulary ➤ Problems with vision	➤ Sudden/gradual onset ➤ May have stroke related/stroke like deficits ➤ May have disturbed/unsteady gait ➤ Loss of bladder and/or bowel control ➤ Slurred speech ➤ Language problems (vocabulary, choice of words, confusion in communication) ➤ Loss of vision in some cases
NEUROLOGICAL AND BEHAVIORAL CHANGES	
➤ Memory impairment especially inability to learn new information or forgetting recently learnt information or events ➤ Progressive memory disorder that worsens with time	➤ Memory impairment ➤ Loss of executive function (Decreased ability to plan, reason and analyze situations/problems, organize thought and behavior) ➤ May be gradual, but typically develops in a stepwise manner or sudden memory loss following a stroke (post stroke dementia) or after series of cerebrovascular accidents
Common symptoms: Depression, Disorientation, Emotional instability, Anxiety, Mood disorder, Confusion with time and place, Attention deficit and general restlessness, Delusions, Inability to comprehend current situations, Social awkwardness and withdrawal	
DIAGNOSIS (Brain imaging techniques)	
Computed Tomography and MRI (magnetic resonance imaging) ➤ Increased beta-amyloid and tau proteins in the brain ➤ Blood brain barrier dysfunction ➤ Neuronal cell damage and death ➤ Decreased communication in the brain ➤ Brain atrophy (whole brain, entorhinal, hippocampal) ➤ Assess structural and volume changes in hippocampus and temporal lobe	CT and MRI ➤ White matter lesions ➤ Hippocampal damage ➤ Small stroke infarcts ➤ Lacunar infarcts
Future direction: *functional MRI and PET (positron emission tomography) imaging hold promise to assess both structural and functional losses in the brain and to better diagnose dementias*	
RISK FACTORS	
➤ Age ➤ Genetics ➤ Hypertension ➤ Cardiac disorders ➤ General health ➤ Diabetes	➤ Age ➤ Stroke ➤ Hypertension ➤ Cardiac disorders ➤ Atherosclerosis ➤ Diabetes ➤ Metabolic syndrome ➤ Genetics

Model		Model Characteristics	Pathophysiology	Limitations
Vessel occlusion models	2 VO or BCCAo	Global chronic cerebral hypoperfusion via permanent occlusion of both CCA's (Common carotid artery)	○ Forebrain ischemia model ○ WM rarefaction ○ Axons and myelin damage ○ Hippocampal (CA1) and cortical neuronal damage ○ Striatal infarctions ○ Increased inflammation ○ BBB disruption (temporary-maximum at 3d) ○ Glial activation (mainly in WM) ○ Oxidative stress	○ Rapid drop in CBF ○ Variable extent of ischemic lesions ○ Vendor and strain based variabilities ○ Damage to visual pathway/retin al perfusion ○ Optic nerve and tract damage may influence cognitive tests ○ Does not follow SVD pathophysiology, and affects microvascular flow via occlusion of both CCA's
	4 VO	Consecutive occlusion of both vertebral arteries and both CCA's	○ Neuronal damage (Cortical, hippocampal) ○ Early neurodegeneration in hippocampus ○ Increased immunoreactivity	○ Is a 2 step-2day procedure ○ Damage to visual pathway/retin al perfusion ○ Variability in surgical procedure ○ Variability in occlusion durations ○ Vendor and strain based variabilities
	UCCAO	Chronic cerebral hypoperfusion via permanent occlusion of a single CCA	○ WM rarefactions (delayed, corpus callosum) ○ Decreased synaptic plasticity ○ Increased inflammatory responses ○ Neurodegeneration (mild)	○ Infarcts may not be histologically detectable ○ Spatial memory and learning are not affected ○ Mild short term memory loss only
	BCAS (*Most promising VaD model*)	Bilateral occlusion of CCA's using a micro-coil (recommended diameter 0.18mm; but may vary from . 16mm–0.22mm)	○ WM lesions and rarefactions in Corpus callosum ○ Increased inflammation ○ BBB disruption ○ Delayed hippocampal damage and atrophy ○ Decreased brain metabolism	○ Complete occlusion of both CCA's in mice increases mortality ○ Delayed WM lesions in mice due to milder CBF reduction ○ CBF variability between strains might affect BCAS effectiveness ○ High mortality, CBF reduction and grey

Model		Model Characteristics	Pathophysiology	Limitations
			○ Gliosis- microgliosis, astrogliosis	matter damage with 0.16mm coil ○ Damage to vessel endothelia ○ Spatial memory is not affected ○ Amyloid beta deposition has been reported ○ Does not follow SVD pathophysiology, and affects microvascular flow via occlusion of both CCA's
Multiple infarcts and Thromboembolism model (*Clinically most relevant model*)		Injection of microemboli into the ICA (internal carotid artery) Emboli: cholesterol crystals / microspheres or microbeads / thrombi Size range: 40 – 100 μm	○ Infarcts in cortex and striatum ○ Microglial, macrophage and astroglial activation ○ Increased inflammation ○ Delayed demyelination ○ Mitochondrial dysfunction ○ Oxidative stress ○ Hippocampal damage ○ Impaired neuro-transmitter mechanisms ○ BBB damage	○ Short term or transient deficits ○ Variability in emboli material, size, numbers makes comparisons difficult
High Fat Diet model		Free feeding of High fat diet (western diet 40% fat, Lard based 60% fat)	○ Hippocampal neuronal damage: Impaired hippocampal synaptic plasticity and loss of dendritic spine density ○ Increased inflammation ○ Oxidative stress ○ Decreased BDNF levels ○ NF-kB activation ○ Metabolic Syndrome	○ Variability in duration of HFD ○ Variability in % of High fat and source of fat
Models using risk factors to induce VaD	**Hypertension**	Stroke prone spontaneously hypertensive rats (SHRSP)	○ Cortical (~80%) and striatal infarcts ○ Hippocampal WM and grey matter decrease ○ Hippocampal astrogliosis	○ Lesion volume and stroke outcome is variable ○ Neurological deficits may influence cognitive testing if selection is not thorough

Model		Model Characteristics	Pathophysiology	Limitations
			○ WM damage with gliosis ○ Inflammatory responses ○ Endothelial injury (causing vessel wall damage and rupture, BBB disruption, micro bleeds) ○ Small vessel wall hardening ○ Edematous injury	○ Regular and careful assessment of animals for neurological stroke like symptoms and body parameters like weight etc throughout the study is required ○ Visual pathway can be affected
	Diabetes	T1DM, T2DM rat and mouse models	○ BBB disruption ○ Hippocampal damage (decreased synaptic plasticity, dendritic density, neurogenesis) ○ Inflammatory responses ○ Oxidative stress ○ Hippocampal microglial activation	○ Careful evaluation of whether VaD or AD has onset is required.