A Synopsis on the Linkage Between Age-Related Dementias and Vascular Disorders

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Abstract: The concept of age-related dementias and vascular disorders has now been recognized for over a century. In the present review, we have emphasized on the causes, consequences and the true bases for the treatment and prevention of these disorders. Systematic efforts have been put together to identify the aetiology in each case. Increased efforts have been targeted towards the concept and genetic factors responsible for vascular cognitive impairment and post-stroke dementia in relation with Alzheimer's disease, which is a consequence of age-related dementia, especially as they hold promise for early prevention and treatment. It has now been well accepted that vascular dementia is not a single disease but a group of conditions with different pathological correlations and pathophysiological mechanisms. The present review represents an amalgamation of several pathophysiological mechanisms producing a very heterogeneous clinical presentation for developing such consequences. We suggest current diagnostic categories and describe clinical parameters according to recently reported studies that document the demographic data in a standardized manner for age-related dementia disorders.

Keywords: Mitochondrial lesion, post stroke dementia, reactive oxygen species, vascular dementia.

INTRODUCTION

Dementia is a concise term used to describe a group of brain disorders that involve chronic deterioration in cognitive function resulting eventually in severe cognitive impairment [1]. Patients with dementia experience a steady decline in their ability to understand, remember, reason, communicate and use learned skills [2]. Mood changes are also very common in dementia, as the part of brain that controls emotion is affected [3]. Epidemiological studies conducted on dementia have highlighted loneliness and social isolation as prominent factors leading to dementia [4]. The impairment of memory and cognitive function due to neuronal death is a common cause of dementia [5]. Aging is the primary risk factor for developing dementia, because loneliness and social isolation arise with increase in the life span [6]. Hence, increased life expectancies lead to an increase in the number of people with dementia disorders. Approx. 1% and 50% of population over 65 and 90 years of age, respectively, are reported to have a dementia disorder [7]. Stress has been reported as an important factor in many processes related to brain [8-15]. Oxidative stress that results in mitochondrial ultrastructural alterations and DNA damage have been postulated to play a key role in neurodegenerative diseases (NDDs) and dementia [12, 16-18].

Dementia is characterized with abnormal behavioral abilities to such an extent that it interferes with a person's daily life and activities [2, 19]. Age related dementia include NDDs and have been reported to be linked other chronic age related diseases [20-22]. According to neurologists, signs and symptoms of dementia may result when once-healthy neurons (nerve cells) in the brain stop working or lose connections with other brain cells and die [23]. Evidences are there stating that everyone loses some neurons as they age but dementia patients experience far greater loss [23]. Clause revealed by scientists working on dementia states that memory loss, though common, is not the only sign of dementia [2]. For a person who is considered to have dementia, he or she must be diagnosed by at least two or more impaired core mental functions including memory, language skills, visual perception, ability to focus and pay attention and cognitive skills such as the ability to solve problems [24]. The loss of brain function in dementia is severe enough that a person cannot do routine daily tasks,

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lose control over their emotions and results in significant changes in personality, accompanied with delusions and hallucinations [23].

Environmental factors may also lead to the development of certain types of dementia [25]. However, this relationship is expected to be complex, since a person may carry genetic mutations that may influence his or her response to environment. Environmental factors like anoxia and a related condition, hypoxia, are terms often used to describe a state in which there is less supply of oxygen to an organ's tissues [24]. Anoxia and hypoxia can lead to the loss of neurons and may lead to diffuse brain injury [25]. Characteristics of the resulting dementia include confusion, personality changes, hallucinations or memory loss, and this type of dementia commonly occurs in people who survive cardiac arrest [24]. Exposure to lead, mercury, other heavy metals, or poisonous substances can also result in dementia [26]. These symptoms may or may not resolve after treatment, depending on how severely the brain is damaged. People who indulge in activities like alcohol consumption and recreational drugs may also display signs of dementia and the symptoms of dementia remain persistent even when he/she stops using it; this condition is known as substance-induced persisting dementia [27].

Vascular dementia (VaD) is defined as the loss of cognitive function resulting from ischemic, ischemic-hypoxic or hemorrhagic brain tissue lesions due to cardiovascular diseases and cardiovascular pathological changes [28]. A recent study gave rise to a new concept which classifies vascular cognitive impairment (VCI) as a syndrome with evidence of clinical stroke or subclinical brain injury and cognitive impairment affecting at least one cognitive domain [29]. Basic pathological factors causing VaD have been correlated to dementia disorders [30]. VaD is also known as VCI, which is not a regular pathogenic disease. Recent researches have demonstrated definitive correlation between neurological disorders and other chronic diseases like cancer [31-35], diabetes [21, 36-38], cardiovascular disorders [39-45]. Citing the remarkable associations and implications of dementia in major diseases and vascular disorders [6, 18, 19, 46], we have compiled a detailed account of linkage between age-related dementia and vascular disorders.

MITOCHONDRIAL LESIONS AND SIGNALLING CASCADE IN VaD

Mitochondria are sites of formation of reactive oxygen species (ROS), including superoxide anion ($O^{2\bullet-}$), highly reactive hydroxyl radical ($OH^{\bullet}$) or its intermediates and reactive nitrogen species such as nitric oxide (NO) [47]. Mitochondria also generate endogenous ROS as by-products of oxidative phosphorylation [48]. Mitochondrial dysfunction and ROS-induced oxidative damage have been implicated in pathogenesis of various neurological diseases [8, 10, 17, 18, 49, 50]. The primary ROS produced by mitochondria is the superoxide anion [51]. Intramitochondrial antioxidant defense systems scavenge this radical to avoid oxidative damage, which can affect ATP production in mitochondria. During aging and related neurodegenerative disorders, damaged mitochondria are unable to maintain the energy demands of the cell [52]. This can lead to an increased production of free ROS which renders oxidative phosphorylation and results in decreased levels of ATP. Decrease in the production of ATP and increase in oxygen species may lead to mitochondrial-dependent cell death [53]. According to a reported study on the association of neurodegeneration with mitochondrial dysfunction and oxidative damage which emerged from animal studies using mitochondrial toxins, these dysfunctions have been strongly implicated in the pathogenesis of human as well as in animal models of NDDs [54]. The effect of acute ischemia and chronic NDDs on neuronal mitochondrial ultrastructure has been documented [55]. The theory which documented that under physiological conditions many redox reactions either reduce or oxidize to NAD(H) means that reactions that consume NAD are catalyzed by NADase enzyme CD38 that primarily control the level of NAD in the brain [56]. This may also include reactions catalyzed by poly (ADP-ribose) polymerases (PARPs), mono-(ADP-ribose) transferases (ARTs), histone deacetylases, and bifunctional ADP-ribosyl cyclases/cyclic ADP-ribose hydrolases [57]. NADase activity in plasma membrane, mitochondria, endoplasmic reticulum, and nuclei was reported to be absent in the brain of CD38-deficient mice, whose tissue NAD level was 10-fold higher than that in wild-type animals [58]. Under pathological conditions, for example, during cerebral ischemia/reperfusion, oxidative stress, hypoglycemia, ammonia toxicity, and glutamate excitotoxicity, the PARP-1 appears to be the most potent NAD-consuming enzyme [58]. PARP-1 becomes highly activated because of its role in facilitating the repair of damaged DNA. Activated PARP-1 hydrolyzes NAD and transfers the ADP-ribose moieties to form poly(ADP-ribose) on acceptor proteins [59]. This activity can potentially lead to dramatic decline in cellular NAD, particularly under metabolically stressed conditions in which a decline in cellular ATP can limit NAD biosynthesis *via* the ATP-dependent NAD synthetase reaction [60]. Once the NAD concentration drops down below approx. 1 mM level necessary to sustain the glycolytic glyceraldehyde-3P dehydrogenase reaction or approx. 0.1 mM level necessary for intra-mitochondrial dehydrogenase reactions, the rate of ATP production is impaired, thus resulting in a vicious cycle that if not reversed eventually results in permanent metabolic failure and necrotic cell death [61]. Depletion of NAD can also result in both necrosis and apoptosis by multiple additional mechanisms, including promotion of mitochondrial permeability transition and modulation of NAD-dependent sirtuins which are protein deacetylases that regulate cell-death genetic programs [62-64]. According to *in vivo* and *in vitro* studies, the long-term ischemia/reperfusion may disintegrate the mitochondrial ultrastructure [65-67].

However, apoptosis of degenerating neurons may occur in association with the accumulation of perikaryal mitochondria and oxidative damage to the nucleus [68]. Similar pattern of mitochondrial lesions is also observed in brain biopsy samples of human Alzheimer's disease (AD) cases [69]. The reduced expression of both mitochondrial and nuclear DNA-encoded genes corresponds with a physiological down-regulation of the mitochondrial respiratory chain in reference to declining neuronal activity [65]. However, the role of somatic cells and mitochondrial DNA mutations in pathogenesis of mitochondria failure

during AD is still controversial [70]. According to recent findings, the mitochondrial abnormalities appear to be key features in the development of AD-like pathology which was conducted in YAC AbPP transgenic mice [55]. In humans, deleted mtDNA is increased at least 3-fold in AD cases as compared to controls [71]. Moreover, it has been reported that mitochondrial DNA isolated from the brains of AD patients shows oxidative modifications containing 8-hydroxy-2'-deoxyguanosine (8OHdG) [72]. Moreover, studies using *in situ* markers for 8OHdG and 8-hydroxy-guanosine (8OHG) showed that RNA oxidation is a reason for damaged neurons in AD [73]. Quantitative analysis revealed a strong positive correlation between mtDNA deletions, cytoplasmic RNA oxidation among age-matched controls (r = 0.9.3.4.) and AD neurons in the early stages of non-reversible damage [74]. However, no correlation existed for AD neurons in the end stages of nonreversible cellular damage [71]. This attributed that end-stage neurons contain only remnants of cytoplasmic organelles and thus, they differ in their amount of mtDNA.

NITRIC OXIDE DEPENDENT PROCESS IN DEMENTIA AND RELATED PATHOGENESIS

NO has significant physiological functions, and NO pathways have been implicated in a number of neurological disorders and other NDDs [75]. NO is generated by endothelial cells in the vascular system [76]. In advanced stages, NO induces the presence of vascular risk factor which causes a decrease in cerebral blood flow *via* microvasculopathy with impaired NO release, and this in turn results in regional metabolic dysfunction [75]. NO operates *via* multiple downstream signaling mechanisms, thus suggesting that at low concentrations NO serves as neuroprotector and mediates physiological signaling (e.g., neurotransmission or vasodilatation) [77]; while at higher concentrations, NO mediates immune/inflammatory actions and exerts neurotoxic effect [78]. It has long been reported that NO could also act as a retrograde messenger at the synapse, mediating transmission from target neurons back onto the synapse and regulating synaptic transmission. Signal transduction can be safely correlated at gene level [79]. It was shown through knockout [KO (potassium oxide), NOS (nitric oxide synthase)–/–)] mice and thus stated the physiological roles of the three NOS genes and their splice variants [80]. According to this experiment, the dominant splice variant is nNOSα, which possesses an amino terminal PDZ domain and associates with N-Methyl-D-aspartate receptor (NMDAR) at postsynaptic densities [81]; whereas nNOSβ lacks this structure and so is less closely coupled to NMDAR-mediated synaptic activity [82]. nNOSγ has little or no enzymatic activity and nNOSμ is similar to nNOSα with an insert around the calmodulin binding motif plasticity [82]. However, the same properties also enable NO to signal to any local compartment and to cells that lack synaptic activity or NOS expression. There is considerable evidence that both eNOS and iNOS contribute to physiology and pathology in the nervous system [83]. Hypertension is the major phenotype in eNOS–/– as endothelial-derived NO is essential to maintain physiological vascular tone and peripheral resistance [84]. eNOS–/– mice are susceptible to cerebral ischemia [85]. It was reported that iNOS induction is predominantly associated with inflammation and disease [86]. Few phenotype of iNOS–/– include decreased lipopolysaccharide–induced microvascular responsiveness to vasoconstrictors (i.e., septic shock) and increased susceptibility to infections, although this strongly depends on the type of infection and affected organ [87]. Expression of iNOS in brain and vasculature is low under physiological conditions, and it has little role in maintaining the vascular tone [82]. The association of iNOS with inflammation proves to be a significant association with pathology, as although iNOS activity is not calcium dependent, the capability to generate NO at micromolar levels provides remarkable pathological potential [88].

NO signaling in brain contributes to various forms of plasticity [long-term potentiation (LTP) and long-term depression (LTD)]; rhythmic activity, including respiratory and circadian rhythms; and locomotor and thalamocortical oscillations [89, 90]. NO is involved in learning and memory in cerebellum [91], hippocampus [92], neocortex [93] and LTD in the cerebellum [94]. LTD in cerebellum is generated on stimulation of parallel fibres, acts post-synaptically in Purkinje cells, and requires the NO/PKG (cGMP-dependent protein kinase) pathway [95]. An interesting link between NO signaling and LTD is given by the actions of G-substrate, a potent inhibitor of protein phosphatase 1 (PP1) and 2A (PP2A), and activated as a result of PKG stimulation [96]. The effects of G-substrate on LTD formation was found to be age dependent, where LTD is only diminished in G-substrate-deficient mice during postnatal five to six weeks [97]. The targets of nitrergic signaling pathways are involved in modulation of presynaptic transmitter release at excitatory glutamatergic and inhibitory GABAergic synapses, postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) phosphorylation and trafficking, calcium channels, potassium channels, and interactions with other signalling pathways (such as mGluR, endocannabinoid, and catecholamine) [82]. The retrograde messenger at glutamatergic synapses is important to rule out in stimulating research, and there is clear evidence for the involvement of NO in LTP in both the hippocampus and cerebellum [98]. Studies have shown a strong relation between NMDAR-mediated calcium influx and nNOS activation (through their mutual PDZ binding) which provides a clear synaptic, activity, and plasticity associated trigger to postsynaptic NO generation [97]. However, much evidence is found to favor postsynaptic rather than presynaptic mechanisms of LTP [99], and so the idea that NO is a retrograde messenger for this form of plasticity is not proven although LTP in cerebellum is suggested to be of presynaptic origin [90].

Further, nitrergic signaling in central nervous system modulates different ion channels, triggering alteration of postsynaptic glutamate receptor and changes intrinsic neuronal excitability *via* phosphorylation or S-nitrosylation of voltage-gated ion channels which include sodium, voltage-gated calcium, Ca^{2+}-activated and ATP-sensitive potassium, and cyclic nucleotide-gated and IH channels [100-103]. The targeting of potassium channels to modulate intrinsic excitability is also related with nitrergic mechanisms in smooth muscle in neurohypophysis/oxytocin regulation [100], and most recently, it has been observed in the auditory brainstem [82, 104]. NO generation on synaptic

activity at the calyx of Held synapse lead to increased postsynaptic cGMP, together with suppression of Kv3 potassium channels [82]. Moreover, this suppression increased action potential duration and reduced the fidelity of synaptic transmission during high-frequency synaptic stimulation [82]. This action was mediated by cGMP-dependent protein kinases and was rendered by NMDAR, nNOS, and sGC antagonists [82]. Kv3 channels, which affect transmitter release by shaping the presynaptic action potentials, are suppressed by NO-cGMP pathway, not through direct phosphorylation by PKG but through the intermediate step of a phosphatase, which dephosphorylates recombinant channel protein in Chinese hamster ovary (CHO) cells [105]. This finding attributes that vascular pathology plays a crucial role in the pathogenesis of so-called neurodegenerative dementias.

INDIVIDUALIZED SPECIFIC GENE MUTATION CAUSING DEMENTIA

The understanding of pathobiology of AD and VaD received an impulse by the discovery of genes that produce monogenic forms of the illness or contribute to polygenic forms [106]. In particular, the identification of genes contributing to VCI would no doubt provide insight into the cellular and molecular basis of VCI [106]. Genetic factors play an important role in the aetiology of VaD; in particular, it seems to be more important in large-vessel stroke and small vessel stroke than in cryptogenic stroke, and there is no epidemiological evidence for a genetic component in cardioembolic stroke [106]. The genes underlying VaD must be of two non-mutually exclusive classes, genes that predispose individuals to cerebrovascular disease, and genes that determine tissue responses to cerebrovascular disease (e.g., genes conveying ischemic tolerance or susceptibility, or the ability to recover from ischemic insult) [106]. In addition, several monogenic forms of cerebrovascular diseases have been identified [107]. The two best studied of these forms are cerebral autosomal dominant arteriopathy with subcortical infarcts and leuco-encephalopathy, Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopath (CADASIL) - a subcortical small vessel disease accompanied by lacunar strokes, migraine, and dementia; and hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) [107]. The CADASIL condition is a heritable small-vessel disease caused by mutations in NOTCH3 gene which is normally expressed in vascular smooth muscle cells and pericytes (including those of the cerebral vasculature) and this gene encodes a cell-surface receptor, which has a role in arterial development and is expressed on vascular smooth-muscle cells [106]. It appears to be involved in directing smooth muscle cell proliferation and differentiation. The NOTCH3 receptor is a heterodimer composed of a large extracellular fragment and a small transmembrane intracellular fragment [108]. About 95% of patients have missense mutations that cluster in exons 3 and change the amount of cysteine residues, but the pathogenic mechanism is still unknown [109]. With regard to HCHWA-D (a syndrome of primarily hemorrhagic strokes and dementia), it is caused by a mutation in the gene for amyloid precursor protein (APP) that causes abnormal deposition of amyloid in the walls of leptomeningeal arteries and cortical arterioles (a pathological condition known as cerebral amyloid angiopathy) [106]. Mouse models have been developed for CADASIL and HCHWA-D and have contributed critical insights into the cell biology of pathogenic processes underlying them [110].

CORRELATION BETWEEN VAD AND OTHER DEMENTIAS

Person suffering with cognitive impairment does not resemble completely to dementia but shows significant impact on quality of life and ability to carry out activities of daily life. Thus, it is very likely that a patient with late-onset AD may already have a vascular burden and sharing with VaD and vascular risk factors. Multiple small thromboembolic strokes or strokes in strategic locations such as thalamus, frontal lobe or temporal lobes may be the cause of cognitive impairment and thus frequently occur without classical stroke-like symptoms, whereas majority of patients suffering from VaD are accompanied by related cerebral damage, which is often clinically silent or is accompanied by unspecific neurological signs [111]. Neurologists have brought up several mechanisms for pathological VaD. According to one of these mechanisms, post-stroke dementia may induce vascular lesions in brain [112]. There is also a belief that post-stroke dementia could be the result of AD's related pre-existing neuropathological effects [113]. However, vessel damage by recurrent strokes may induce white matter lesions that may lead to cognitive decline and may contribute to post-stroke dementia [114].

Recent study has revolved around important roles of amyloid beta (Aβ) peptide in cognitive impairment and dementia [115]. In view of this, we have thrown light on exact mechanism that underlines its role in VaD. In VaD, the supply of substrates and oxygen to active neurons slowed down which attributed in alterations in the cerebral microenvironment and neuronal dysfunction [116]. Alterations in cerebrovascular autoregulation have important implications for functional and structural integrity of the brain [117]. Loss of autoregulation renders brain more susceptible to reductions in arterial pressure, such as those occurring in sleep [117]. Thus, reductions in arterial pressure that would not alter cerebral perfusion in normal brain may lead to cerebral ischemia in the presence of Aβ [117]. Hypoperfusion-related ischemia would be the hallmark in periventricular white matter, a region supplied by arterioles with limited collateral flow [118]. Thus, patients with AD are rendered with impairment in autoregulation that could contribute to the periventricular white matter lesions [119]. Furthermore, data from several clinical studies emphasized that the presence of ischemic lesions have pronounced cognitive deficit effects in patients with AD pathology [120-122]. Thus, cerebral ischemia is responsible for worsening the effects of AD pathology on cognitive function [123]. Experimental data suggested that cerebral ischemia upregulates the expression of APP in healthy rats [124]. Furthermore, in correlation with Aβ peptide, it was reported that ischemia enhances the cleavage of Aβ peptide from APP. Therefore, the ischemic process enhances Aβ cleavage, thereby amplifying cytotoxicity [125]. Aβ could also be responsible for enhancing the release of inflammatory mediators that exacerbate post-ischemic inflammation and

contribute to cerebrovascular dysfunction [126]. Although it is unknown whether ischemia-induced Aβ production leads to amyloid plaque formation, the reports on APP mice without plaques suggest that non-deposited Aβ is sufficient to produce vascular and cognitive impairment [127]. This is in accordance with the suggestion that Aβ oligomers rather than amyloid plaques are responsible for the neuronal dysfunction and cognitive impairment [128]. Moreover, the alterations of small vessels play an important role in causing damage to the cerebral tissue and are potentially responsible for subsequent development of cognitive alterations [106]. Small vessel lesions are considered to be related to deep lacunar infarcts and white matter changes, typically observed in subcortical forms of VCI [129].

THERAPEUTIC STRATEGIES

There has been dearth of literature available on therapeutic strategies for various dementia conditions. Stroke is an important precursor of VaD [130]. A question arises whether modifications of risk factors for stroke such as hypertension, hyperlipidemia or dyslipidemia, atrial fibrillation, or diabetes play any role in disease risk management or improve cognition in individuals with VaD [131]. Statins are a class of drugs that upregulate low-density lipoprotein (LDL) receptor activity and increase high-density lipoprotein (HDL) cholesterol, which have been associated with elevated VaD risk by inhibiting 3-hydroxy- 3-methylglutaryl coenzyme A (HMG-CoA) reductase thereby reducing formation and entry of LDL cholesterol particles into circulation [132].

Another popular drug, galantamine, is a cholinesterase inhibitor that like other similar drugs of this class, has a regulatory approval for treatment of AD [133]. RCTs involving VaD patients were selected for meta-analyses [134]. VaD and AD patients showed radiological and historical evidences of cerebrovascular disease [46]. Galantamine at 24 mg/day for 24 weeks did not significantly change any of the outcome measures in VaD subgroup of subjects [30]. It was reported that although galantamine seems to improve cognition in VaD patients, it does not have a documented global clinical benefit [135]. This may be attributed to the presence of side effects suggesting caution in prescribing galantamine to patients with VaD. Donepezil, another acetylcholinesterase (AChE) inhibitor, was studied in three large-scale RCTs that enrolled 2193 patients with probable or possible VaD diagnosed according to NINCDS-AIREN criteria [136]. Compared to placebo, donepezil showed a beneficial effect on cognitive function, global assessment, and activities of daily living (ADL) [136]. Both 5 mg and 10 mg daily doses were shown to be effective in most, but not all measures. Clinical Dementia Rating (CDR) and Alzheimer's disease Functional Assessment and Change Scale (ADFACS) ADL ratings, did not improve at 5 mg dose but there was a significant improvement at 10 mg/day. ADL showed more improvement in global function among participants taking 5 mg of donepezil daily compared to the placebo group but this was not seen in 10 mg/day dose group. Side effects were more pronounced in donepezil group, especially in 10 mg/day group. Although meta-analysis didn't show higher risk of death in donepezil group compared to placebo, the risk of death got significantly increased with intake of donepezil compared to placebo in trial "319" [1.7.% (11 of 648 subjects) donepezil *vs* 0% (0 of 326) placebo] [136, 137]. This study did not entirely rule out possibility that a proportion of enrolled patients had AD rather than VaD, and that the beneficial effect of drug was due to its activity directed at AD-related neuropathology rather than at pathological changes underlying VaD.

Rivastigmine is a non-specific inhibitor of AChE and butyrylcholinesterase [138]. It has a regulatory approval for AD and Parkinson's disease dementias. One large-scale RCT enrolled 710 patients with VaD for this purpose [139]. Exploratory analyses showed that improvement in cognition was more pronounced in older subjects and likely represented the known drug effect on concomitant AD pathology more prevalently in older patients [140]. This finding supports the existing argument that putative cholinergic deficit in VaD reflects the presence of concomitant AD pathology [139]. *Ginkgo biloba* extract has a combination of effects that include protection of neuronal and myocardial cells against ischemia, increasing blood supply, reducing blood viscosity, modification of neurotransmitter systems, and reducing oxygen free radicals [132]. Recent studies meta-analysis has shown a change in cognitive scores in favour of gingko compared to placebo in patients with AD, VaD or mixed dementia [141]. Huperzine A, a naturally occurring AChE inhibitor and NMDAR antagonist [142], has a mechanism of action similar to donepezil, rivastigmine, and galantamine, and has been considered as an alternative treatment for VaD. A significant beneficial effect of Huperzine A was observed on daily living activities after six months of treatment. No deaths were reported from any cause at the end of treatment. Behavior, quality of life and caregiver burden were not assessed in this trial. There is currently no high quality evidence to support the use of Huperzine A for treatment of VaD [142]. Finally, it can be suggested that AChE inhibitors- donepezil, galantamine, and rivastigmine may have modest beneficial effects on cognitive symptoms of VaD without a concomitant global or clinical benefits in most cases. Apart from various therapeutic strategies mentioned, recent researches have highlighted new methods of drug development viz., region-specific treatment strategy [143], machine learning approaches [144], and support vector machine, artificial neural network and bayesian classifier [145], to name a few. Moreover, age-related dementia and VaD can also utilize modern therapeutic options like proteomics approaches [38, 146, 147], glycoprotein interaction studies [31, 39, 41-43, 148-150] and novel nanotechnological approaches [32, 147, 151, 152].

CONCLUSION

Data from humans, animal and *in vitro* studies suggests that sources of antioxidants, phytochemicals (flavonoids, flavonols, phenolic acids and terpenes, derived from plants) have a beneficial role with respect to brain aging and NDDs by possessing anti-oxidative, anti-inflammatory, anti-viral, anti-proliferative, and anti-carcinogenic properties. The conclusion that treatment of hypertension may reduce VaD risk and attenuate its progression is clinically important. However, more research will be needed before it could be translated into treatment and prevention. It is not known at

present if anti-hypertensive treatment could reduce VaD risk or modify the disease in carriers of the risk allele. The answer to this and similar questions would require designing a protocol which contains patient stratification by their genotype. Such studies in future will no doubt increase likelihood of developing effective VaD therapeutics.

LIST OF ABBREVIATIONS

Aβ	=	Amyloid beta
AchE	=	Acetylcholinesterase
ADL	=	Activities of daily living
CADASIL	=	Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopath
HCHWA-D	=	Hereditary cerebral hemorrhage with amyloidosis-Dutch type
LTD	=	Long-term depression
LTP	=	Long-term potentiation
NO	=	Nitric oxide
NOS	=	Nitric oxide synthase
PARP	=	Poly (ADP-ribose) polymerase
ROS	=	Reactive oxygen species
VCI	=	Vascular cognitive impairment
VaD	=	Vascular dementia

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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