Vascular dementia - A Narrative Review

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Abstract

Vascular dementia is the second commonest dementia occurring in the elderly above 65 years. The vascular changes within the brain are suggested to be the main etiologic factor for this type of dementia. Clinically, vascular dementia closely resembles Alzheimer's dementia. The present literature review focuses on the clinical features, diagnostic criteria, pathophysiology, risk factors and the management of vascular dementia.

Keywords: Vascular Dementia, Cognitive Impairment, Neuropathology, Biomarkers

Introduction

The incidence and prevalence of dementia amongst the older population have escalated immensely over the past decades around the globe. Dementia is a type of neurodegenerative disorder that leads to cognitive impairment. It is primarily caused by Alzheimer's disease (AD) and vascular eccentricities in the brain, with a prevalence of 60% and 20% of all dementia cases, respectively (Kalaria et al., 2008; Forette & Boller, 1991). Vascular Dementia (VD) is the cognitive disarray of the brain elucidated by vascular changes such as stroke and ischemia, thereby preventing the brain's normal functioning. Along with cognitive impairment, VD is characterized by progressive memory deterioration and gradual decline in performing day-to-day activities.

The clinical signs and symptoms of AD and VD are similar, with considerable overlap in pathophysiology and risk factors. However, a detailed clinical evaluation that reveals ischemic or haemorrhagic brain changes will enable the clinician to confirm the diagnosis. A study in 2007 employed various radiographic aids and brain MRI to investigate the cerebral changes in dementia and suggested that almost 80% of patients with AD showed vascular changes (O'Brien, 2007). After analyzing the theories relative to dementia, the Diagnostic and Statistical Manual (DSM-5) criteria changed vascular dementia to vascular neurocognitive disorder (Plassman et al., 2007; Blackman, 2016). This narrative review will focus on the diagnostic criteria, pathophysiology, epidemiology, risk factors, and a brief note on differential diagnosis and management.

History

The pathophysiology of VD has constantly been evolving over the past century. The narration of cognitive impairment due to vascular disorders within the brain was primarily documented in the early 1600s, and it was referred to as senile dementia until the 1960s. Initially, senile dementia was believed to be exclusively instigated by arterial sclerosis of the cerebral cortex. However, in 1969 Tomlinson, Blessed, and Roth recognized AD as the primary aetiology of dementia that occurs at later stages of human life (Tomlinson, Blessed, & Roth, 1970). The DSM-4 suggested that vascular disease of multiple large infarcts in the cerebral cortex led to dementia (Spitzer, Williams, & Gibbon, 1990). Nevertheless, in due course, it was found that the factor mentioned above is just one among many causes of VD, with subcortical disease essentially accounting for most of the cases of dementia. This warranted a prerequisite for developing new criteria for VD and a criterion for a subgroup of subcortical VD that includes Binswanger's disease (subcortical leukoencephalopathy).

Diagnostic Criteria

1. The original Hachinski Ischemic Scale (Hachinski et al., 1975):
In this scale, a 1- or 2-point value to every medical condition is assigned, and the aggregate of these points gives the final Ischemic Score (Table 1).
2. The criteria proposed by the DSM-III, DSM-III-R, DSM-IV, and DSM-5
Various sets of DSM criteria necessitate the impairment of memory and other cognitive functions to arrive at the diagnosis of VD. The cognitive deficits should be severe enough to trigger the impairment of basic and social functioning. Among these, the criteria proposed in DSM-5 are currently used (Table 2) (Blackman, 2016).
3. Vascular Behavioural and Cognitive Disorders (VASCOG) (Sachdev et al., 2014)
While DSM-5 is a more sensitive diagnostic tool, VASCOG is another tool that is harmonious with DSM-5 and provides better clarity to arrive at a clinical diagnosis (Table 3).
4. The National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (Román et al., 1993)
Criteria for diagnosing VD must be consistent, effective, and easily applicable for clinical and research purposes. To satisfy these requisites, NINDS-AIREN summoned an International Workshop and proposed various criteria for diagnosing VD (Table 4).
5. The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) diagnosis guidelines (Table 5) (Bir, Khan, Javalkar, Toledo, & Kelley, 2021)

Pathophysiology

As the age progresses, gradual changes and disruption of the cortical vascular structure predispose to the development of the disease process (Figure 1) (Bir, Khan, Javalkar, Toledo, & Kelley, 2021). This embraces (but is not limited to) the changes in brain size, arterial stiffness, atherosclerosis (chronic hypoperfusion), and disruption in the function of the blood-brain barrier by neuro-inflammatory molecules that are introduced by vascular risk factors. Moreover, incidence of intracerebral haemorrhages and blood vessel leakage due to the rupture of small arteries also contributes to the pathophysiology of VD.

Epidemiology, prevalence and incidence:

Worldwide assessments reveal that every 20 years, the incidence of dementia doubles, conferring a projection of 115 million people to be affected with dementia by the end of 2050 (Prince, Guerchet, & Prina, 2013). VD is the second commonest type of dementia that appears typically after the age of 65 years. The prevalence increases steeply with an increase in age. It shows slightly greater predilection towards the male gender and African-American race. VD might be more prevalent than AD in Japan and other Asian countries (Ferri et al., 2005). Figure 2 depicts the prevalence and frequency of various types of dementia (Knapp et al., 2007)

The occurrence of cerebrovascular disorders such as micro and macro-infarcts, white matter (WM) lesions, micro-haemorrhages, lacunar infarcts, leukoaraiosis, superficial haemosiderosis, posterior intracerebral haemorrhages, and strategic strokes tend to intensify the risk of acquiring dementia that is independent of AD-associated pathology.

Risk factors

The risk factors for VD are broadly categorized as modifiable and non-modifiable factors.

i. Modifiable risk factors:
Systemic diseases like uncontrolled diabetes mellitus, hypertension, cardiovascular diseases such as arrhythmias, carotid artery stenosis, dyslipidemia, homocysteinemia; lifestyle factors such as obesity and metabolic syndrome, stress, smoking, and alcohol abuse are the modifiable risk factors for VD. Proper treatment and control measures will eliminate or reduce the disease severity and thereby decrease the risk of developing VD.
ii. Non-modifiable risk factors:
Old age increases the risk of developing the disease, with the risk doubling every 5.3 years once the individual has crossed 60 years (Blackman, 2016; Prince, 2013). Genetic factors such as the presence of notch 3 genes for CADASIL, HTA1 gene for CARASIL, GLA gene for Fabry, and apolipoprotein E4 allele (ApoE4) increase the probability of acquiring the disease (Khan, Kalaria, Corbett, & Ballard, 2016) Other non-modifiable risk factors include post-menopausal women, lower-socioeconomic status, and previous history of cerebrovascular diseases such as stroke.

Table 1 - Hachinski Ischemic Scale Score (IS-S)

Medical feature	Score
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2
IS-S ≤ 4 recommends a diagnosis of AD IS-S ≥7 (IS-S 4- 10) suggests a diagnosis of multi-infarct VD. An intermediate Hachinski IS-S of 5– 6 implies a diagnosis of mixed dementia.	

Table 2 - DSM-5 for the diagnosis of VD

A. The criteria are met for major or mild neurocognitive disorder. B. The clinicalfeatures are consistent with avascular aetiology, as suggested by either of the following: 1. Onset ofthe cognitive deficits istemporally relatedto one or more cerebrovascular events. 2. Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function. C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits. D. The symptoms are not better explained by another brain disease or systemic disorder	
Probable vascular neurodegenerative disorder	Possible vascular neurodegenerative disorder
1. Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported). 2. The neurocognitive syndrome istemporally related to one or more documented cerebrovascular events. 3. Both clinical and genetic evidence of cerebrovascular disease is present	This diagnosis is made if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.

Table 3: Criteria for VASCOG

Mild Cognitive Disorder: A. Acquired deterioration in functioning from the previous level of performance in one or more cognitive domains as evidenced by the following: a. Concerns of a patient, knowledgeable informant or a clinician of mild levels of decline from a previous level of cognitive functioning. b. evidence of modest deficits on objective cognitive assessment based on a validated measure of neurocognitive function. B. The cognitive deficits are not sufficient to interfere with their day-to-day activities, but greater effort, compensatory strategies, or accommodation may be required to maintain normal functioning.
Dementia* or Major Cognitive Disorder: A. Evidence of substantial cognitive decline from a documented or inferred previous level of performance in one or more of the domains outlined above. Evidence for decline is based on: a. Concerns of the patient, a knowledgeable informant, or the clinician, of significant decline in specific abilities; and b. Clear and significant deficits in objective assessment based on a validated objective measure of neurocognitive function in one or more cognitive domains. These typically fall two or more standard deviations below the mean of people of similar age, sex, education, and sociocultural background, when a formal neuropsychological assessment is available, or an equivalent level as judged by the clinician. B. The cognitive deficits are sufficient enough to interfere with independence
Note that the DSM-IV and ICD-10 concept of dementia requires deficits in at least two domains, one of which is memory.

Table 4: NINDS-AIREN criteria for the diagnosis of VD

1. Probable vascular dementia: i. dementia syndrome not due to delirium, psychosis, aphasia or sensorimotor impairment, and ii. cerebrovascular disease defined by the presence of focal neurological signs and evidence of relevant cerebrovascular disease by brain imaging (further specified), and iii. a relationship between 1 and 2, such as dementia occurring within three months of a stroke, or abrupt deterioration, or fluctuating stepwise progression.
2. Features consistent with probable vascular dementia include early gait disturbance, frequent falls, early urinary symptoms, pseudobulbar palsy, personality and mood changes, subcortical deficits such as psychomotor retardation, and abnormal executive function.
3. Features making vascular dementia unlikely include clinical symptoms in the absence of focal neurological signs or cerebrovascular lesions on brain CT or MRI.
4. Possible vascular dementia: Possible vascular dementia may be diagnosed in the absence of brain imaging studies or a clear temporal relationship of dementia to stroke.
5. Definite vascular dementia: This requires clinical criteria for probable vascular dementia and pathological evidence of cerebrovascular disease in the absence of tangles and plaques or other types of dementia pathology.

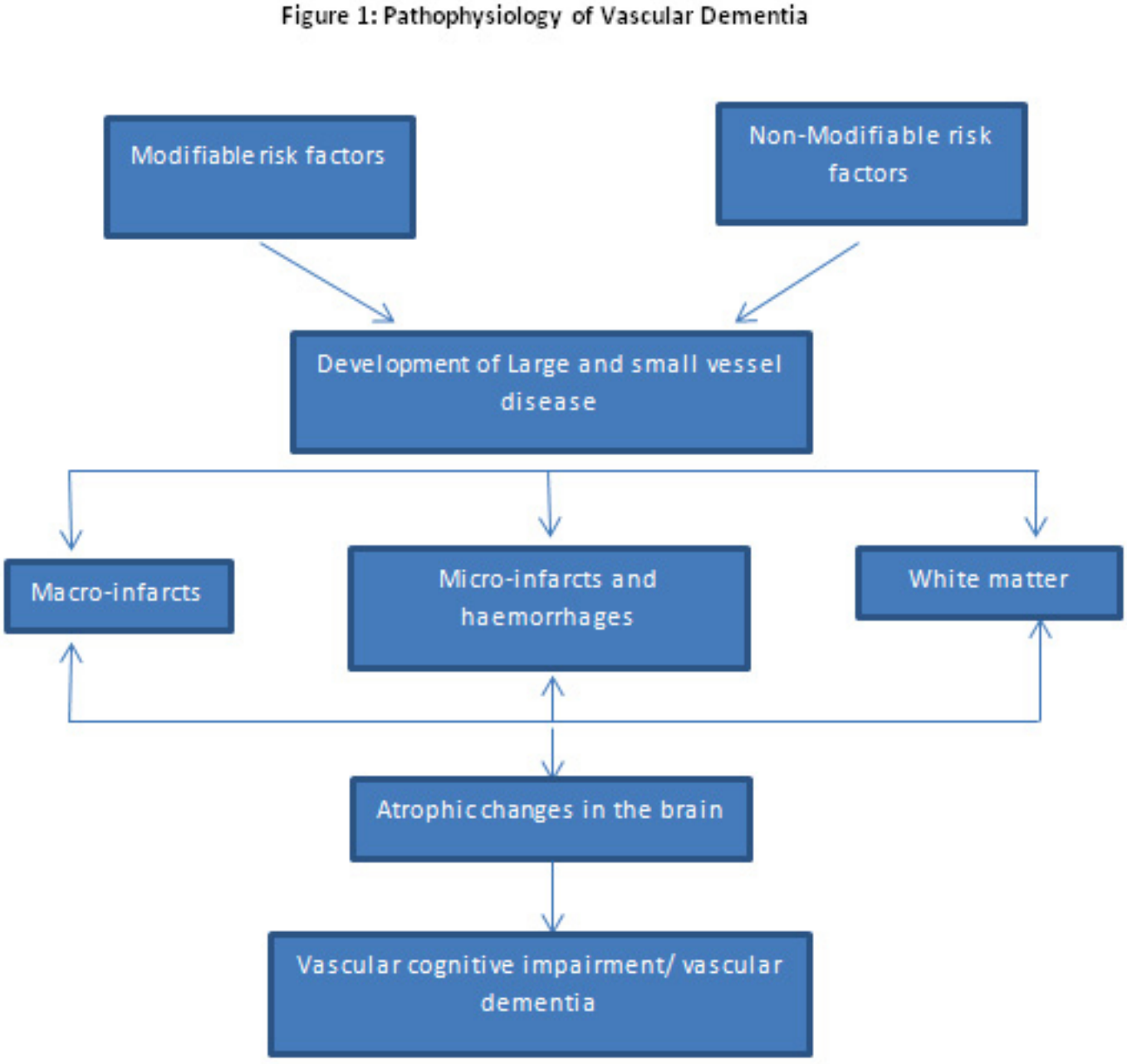
Table 5 - The diagnostic criteria proposed by VICCCS

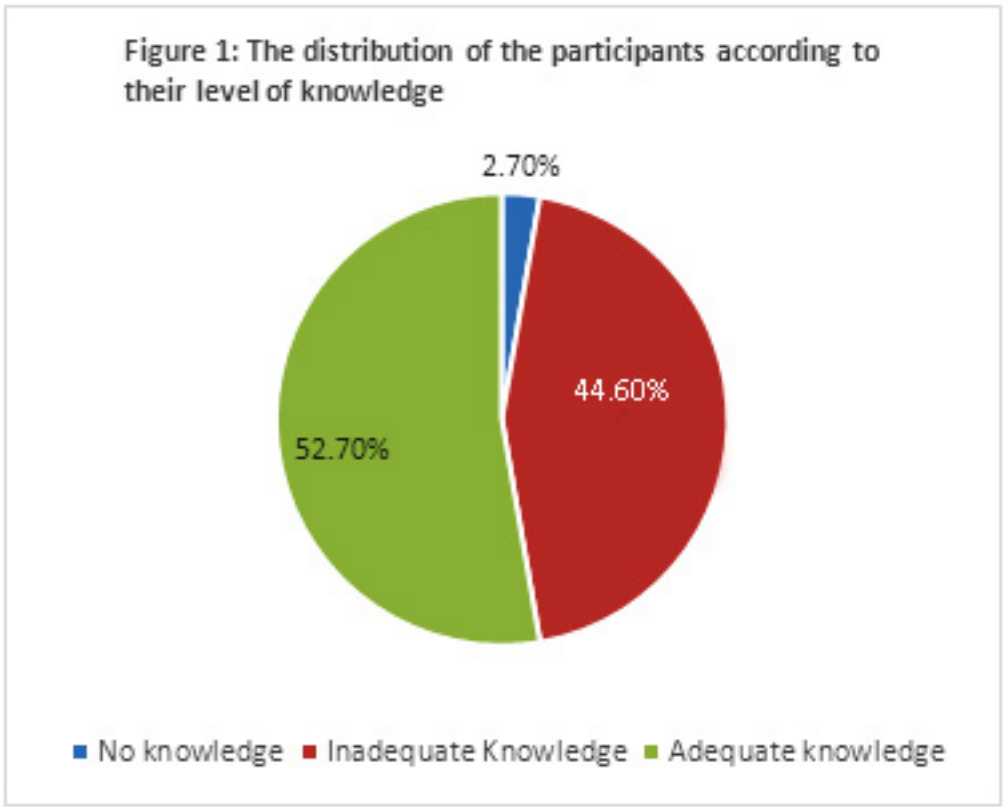
Mild VCI: Impairment in at least one cognitive domain and mild to no impairment in instrumental activities of daily living (IADLs)/activities of daily living (ADLs), respectively.
Major VCI (VD): Clinically significant deficits of sufficient severity in at least one cognitive domain (deficits may be present in multiple domains) and severe disruption to IADLs/ADLs (independent of the motor/sensory sequelae of the vascular event).
Patients given a diagnosis of major VCI (VD) are subcategorized according to the underlying pathology as appropriate. A clear temporal relationship (within six months) between a vascular event and the onset of cognitive deficits is only required for a diagnosis of post-stroke dementia (PSD). Subtypes of major VCI (VD):
i. Post-stroke dementia: A patient described as having PSD may or may not have presented evidence of mild cognitive impairment before stroke.
ii. Mixed dementias: A standalone umbrella subgroup termed "mixed dementias" includes phenotypes representing each combination between vascular and neurodegenerative disease, that is, VCI-AD, VCI–dementia with Lewy bodies, and so forth
iii. Subcortical ischemic VD: Small-vessel disease is the main vascular cause of subcortical ischemic vascular dementia This diagnosis incorporates the overlapping clinical entities of Binswanger's disease and the lacunar state.
iv. Multi-infarct dementia: Multi-infarct dementia is used to indicate the presence of multiple large cortical infarcts and their likely contribution to the dementia. "Probable" and "possible"—terms for the availability of evidence:
Magnetic resonance imaging is a "gold-standard" requirement for a clinical diagnosis of VCI. Probable mild VCI or probable major VCI (VD) is the appropriate diagnostic category if computed tomography imaging is the only means of imaging available.
Those at risk of VCI: It is recommended that greater consideration for diagnosis be given to people who are at risk of VCI if they present with at least six months of sustained impairment (even if very mild), rather than transient impairment, as identified through caregiver reporting and clinical observation. All other potential causes of sustained impairment (e.g., depression or vitamin D deficiency, in addition to the already agreed exclusions from diagnosis) should have been excluded.
Exclusions from diagnosis: Drug/alcohol abuse/dependence within the last three months of first recognition of impairment or delirium.

Table 6 - Subtypes of VCI

Condition	Imaging and pathological changes
Multi-infarct dementia (Cortical VD)	Multiple cortical infarcts
Small vessel dementia (Subcortical VD)	Lacunae, extensive WM lesions; pathological infarcts, demyelination and gliosis
Strategic infarct dementia	Infarct in strategic location (e.g., thalamus)
Hypoperfusion dementia	Watershed infarcts, WM lesions; pathologically incomplete infarcts in white matter
Haemorrhagic dementia	Haemorrhagic changes may be associated with amyloid angiopathy
Hereditary vascular dementia (CADASIL)	Multiple lacunae and WM lesions, temporal lobe WM affected
Alzheimer's disease with cerebrovascular disease (CVD)	Combination of vascular changes and atrophy, especially medial temporal lobe; pathological mixture of vascular and degenerative (plaque and tangle) pathology

Figure 1: Pathophysiology of Vascular Dementia





AD- Alzheimer's disease;
VD- vascular dementia;
DLB- dementia with Lewy bodies;
FTLD- frontotemporal lobar dementia

Protective factors

Higher education and socioeconomic status, multilinguistic individual irrespective of the educational status, healthy lifestyle, non-smoker, and lower level of alcohol consumption have a protective effect as opposed to the development of VD. Statins are the drugs used to counteract dyslipidemia by the HMG-CoA reductase mechanism that reduces the triglycerides and low-density lipoprotein levels in the blood. A systematic review and meta-analysis suggested that the use of statins significantly reduces the risk of developing dementia in the later stages of life (Poly et al., 2020).

Physical activity safeguards neuronal function as well as brain structural integrity. However, cognitive activity bolsters the performance of the neural circuits, thereby promoting the cognitive reserve. The two mechanisms (physical and cognitive activity), when conjoined, reduce the risk of acquiring dementia (Cheng, 2016).

Oestrogen hormone therapy, though initially hypothesized to have protective roles against dementia, is now found to have no significant implication on reducing the risk of dementia. A study by Henderson VW in 2014 highlighted that the use of oestrogen hormone therapy commenced after the age of 65 years may increase the risk of dementia (Henderson, 2014). Likewise, a meta-analysis report in 2005 hinted that the use of NSAIDs did not provide any substantial benefit in reducing the risk of dementia (De Craen, Gussekloo, Vrijsen, & Westendorp, 2005).

Subtypes of Vascular Dementia

Even though the contemporary criteria permitted the recent and novel studies on treatment perspective to be carried out, the validity of the term VD was questioned by many physicians. This prying was fundamental because the definitions of dementia were constructed on the concept of Alzheimer's dementia but did not consider the other types of dementia. Though both types of dementias show cognitive impairment as the key feature; the concept of memory deterioration was not considered while naming VD. Though the term dementia is decidedly apposite for AD, memory loss is inconsistently associated with VD. Therefore, a more inclusive term, vascular cognitive impairment (VCI), was advocated and favoured by physicians and researchers (O'Brien et al., 2003; Hachinski, Iadecola, & Petersen, 2006).

VCI identifies the diverse disposition of the influence of vascular pathology towards the pathophysiology of dementia, as well as classifies the disease into various subtypes (Table 6) (O'Brien & Thomas, 2015).

1. Multi-infarct (cortical):
In this subtype, multiple cortical infarcts with cerebral amyloid angiopathy are noted in most of the cases. Nevertheless, not all infarcts in the diagnosed cases lead to functional cognitive impairment. Among the multiple cortical infarcts, the highest prevalence is seen in the anterior and posterior cerebral artery territory (bilateral presentation), parietal-temporal and temporal-occipital association areas of the dominant hemisphere-including the angular gyrus, the paramedian thalamic region, and inferior medial temporal lobe of the dominant hemisphere (Esiri, Wilcock, & Morris, 1997).

Moreover, the Watershed infarction of the dominant portion of the frontal and parietal lobe in the border zones between tissues that have primary blood supply from the anterior, middle and posterior cerebral arteries is also frequently recounted.

Cerebral amyloid angiopathy (CAA) is the accumulation of β-amyloid plaques within the small and medium-sized blood vessels that predominantly supply the cerebral cortex and the leptomeninges. It is usually diagnosed when numerous micro-haemorrhages are noticed in the brain during an MRI scan (Attems, Jellinger, Thal, & Van Nostrand, 2011). Though CAA is asymptomatic, it might cause cerebral infarction and haemorrhage. As a result of these changes, ischemia of the brain can occur that could lead to the development of dementia and other transient neurologic events. CAA is spotted to be one of the morphologic trademarks of AD. Additionally, it is also identified in the human adult brains without any signs of cognitive disorder.

2. Small vessel dementia (a subcortical ischemic form of VD):
This subtype has an onset above the age of 60 years that shows gradual progression in the disease process. It is frequently linked with hypertension, history of stroke, large vessel diseases, and diseases of the heart valves. Autopsy examination shows destruction of the small blood vessels and nerve fibres of WM, extensive WM lesions, lacunes, infarcts, demyelination, and gliosis. The main clinical features suggestive of this subtype are decelerated processing speed, dysexecutive syndrome, reduction in motor signs, urinary disturbances, and affective disorders. Cognitive deficits or changes seen in this type are short-term memory impairment, altered behaviour, and lack of attention, organization, and decision making (Yamamoto, Craggs, Baumann, Kalimo, & Kalaria, 2011)

This subtype is further classified into Binswanger's disease (i.e., diffuse WM lesions) and multiple lacunar infarcts. In contrary to the features of AD, there are extensive WM lesions, less severe hippocampal atrophy, and absence of Cerebral amyloid angiopathy, which demarcates this subtype of VD from that of AD.

Deep WM vascular changes ensuing subcortical presentation is the widespread type/form. The condition commences rather prematurely in life and is liable to develop a chronic course. The symptoms comprise gait disturbances, Parkinsonism, bradyphrenia, abulia, emotional instability and depression, urinary incontinence, dysphagia, dysarthria, and akinetic mutism. Neuropsychological shortfalls are noted in the aspects of attention, information processing, and set-shifting.

3. Haemorrhagic dementia:
Examination of the brain shows haemorrhagic changes and CAA. The effects depend on the location of the infarct, and various investigations reveal focal neurological findings (Ishikawa, Yanaka, Sugimoto, Ayuzawa, & Nose, 2002).

4. Hereditary vascular dementia (CADASIL):
It is an autosomal dominant type of micro-vasculopathy that is caused by NOTCH 3 mutations of chromosome 19. The age of onset ranges between 20 and 40 years (Peters, Opherk, Danek, Ballard, Herzog, & Dichgans, 2005). The patients usually present with symptoms like depression or migraine with aura. The brain of the affected person shows multiple lacunes and WM lesions (temporal WM) (Charlton, Morris, Nitkunan, & Markus, 2006; Buffon et al., 2006). Nearly 70-80% of the individuals develop mild progressive executive dysfunction much earlier that remains undetected till the fifth decade of life. 60% of the patients have dementia that is possibly diagnosed by the symptoms such as difficulty in walking, personality and mood changes, disturbances in gait and balance, urinary incontinence, and pseudobulbar palsy. Furthermore, recurrent transient ischemic attacks (TIAs), lacunar and subcortical WM ischemic strokes, and strokes in multiple vascular territories are often noted in this subtype. Depression, psychosis, seizures, and other focal neurologic deficits may also occur. In the later years, the patients may develop apathy that is sometimes misinterpreted as depression.

Parenchymal injury, lacunar infarcts, and WM hyperintensities in the frontal and the anterior temporal lobes are significant findings during neuroimaging.

5. Mild Neurocognitive Disorder (MNCD) - AD with CVD:
Here, there is combined vascular change and atrophy of the cerebral cortex, especially the medial temporal lobe. Both vascular pathology and formation of senile plaques and neurofibrillary tangle formation are noticed in this type. The cognitive impairment observed here has multifactorial aetiology. To locate the lesions and identify the aetiology, autopsy examination plays a key role, as the causes coexist.

Vascular disease can coexist with AD and sometimes with Lewy bodies. More often than not, there is going to be mixed pathology. The possible combinations of the pathologies include plaques, tangles with vascular disease, and Lewy bodies. Therefore, it is mandatory to diagnose precisely so that management of the disease is focused on the type of dementia and the specific aetiology.

Differentiating VD from AD:

VD shows the stepwise progression of the disease with less prominent cognitive symptoms. The neurological signs recurrently noted during examination are aphasia or speech difficulties. Frontal symptoms such as apathy, irrational behaviour, verbal fluency problems, and perseveration are apparent if the frontal lobe is involved. Moreover, disturbance in the memory registration phase and impairment in episodic memory, as seen in AD, is absent in VD (Henderson, 2014; De Craen, Gussekloo, Vrijsen, & Westendorp, 2005).

Assessment

One can arrive at a diagnosis as VD after taking a thorough history and performing complete psychiatric & neurologic examination, which includes cognitive testing and brain imaging.

i. History:
Dementia is a clinical diagnosis that ultimately depends upon the clinician's judgement and mandates thorough history taking to identify if the intellectual deterioration has occurred. Clinicians must evaluate the patient's present condition for any debilitating diseases and relevant medication, habits such as smoking, alcohol and sedative use, ADLs and IADLs such as the ability to drive and live and function independently on a daily basis.

ii. Neurologic examination:
It is the most frequently employed as it aids in recognizing the gross focal lesions such as cortical infarcts, and WM damage relating to small vessel disease in the brain (Hachinski, Iadecola, & Petersen, 2006). Estimation of the level of cognitive impairment is a vital part of dementia assessment and is thought to be a feeble connection for the diagnosis of dementia. Neurologic assessment of cognitive and behavioural changes of VCI patients is the same as the assessment of any other patient with alleged cognitive impairment. However, in VCI, the cognitive deficits might encompass any cognitive domain.

The common manifestations of VCI that are revealed during examination are dysexecutive disorder, dysphrenia, impairments in the capability to perform various tasks, and processing and retaining memory (Hachinski, Iadecola, & Petersen, 2006).

iii. Brain imaging:
Brain imaging is an indispensable component for the assessment of patients with impaired cognitive functions and in cases of suspected brain injury due to vascular damage.

MRI is the favoured imaging tool that is exercised to obtain evidence for the signs, location, and extent of any vascular pathology. It is better at spotting lacunar infarcts and micro-haemorrhages. Furthermore, it is helpful in clarifying the diagnosis when confusion exists in identifying the various types of dementias. VICCCS recommends MRI as the gold standard for clinical diagnosis (Bir, Khan, Javalkar, Toledo, & Kelley, 2021)

The clinical implication of WM changes has not been completely explicated. There is a significant association between the CVD risk factors and the incidence of WM changes. Age is considered to be the second strongest

risk factor, only next to hypertension (Schmidt et al., 1992; Breteler et al., 1994). Therefore, WM changes associated with age were referred to as "age-related white matter changes" (ARWMC).

A rating scale proposed by Wahlund LO et al. assessed the severity of white matter changes using ARWMC and compared the results of the images obtained using CT and MRI (Wahlund et al., 2001). The comparison between the two imaging modalities suggested that MRI was a better choice as it detected even the small WM changes.

T2 weighted MRI can envisage various vascular pathologies, including ischaemic lesions, smaller lacunar infarcts, and periventricular leukoaraiosis. Furthermore, it can ascertain the micro-haemorrhages, which is a common finding in the course of CAA.

Additionally, molecular imaging plays a less vital role when compared to its role in detecting the other variants of dementia. However, FDG- PET might be useful in registering certain areas of hypometabolism that can be correlated with the lesions seen on structural imaging.

Clinical features

VD usually presents with a subtle onset of cognitive impairment that shows a gradual stepwise progression of the disease. Initially, memory impairment may show a plateau-like presentation. Complaints relevant to cognition include being responsive to cues and reminders, struggle in forming sentences and language processing, but the patient struggles to form sentences and process languages, experiences attention deficit in terms of difficulty with organization, and solving complex problems. Concentration issues such as decelerated thinking and easy distractibility are also frequently present. The vascular changes are proposed to be the contributors to clinical dementia. Changes in mood or behaviour are also noted, with nearly 25% of the affected individuals suffering from depression. Other symptoms include hallucinations, delusions, motor function deficits such as disturbances in gait, balance, tremors, and generalized weakness.

A study evaluated the effect of depression on the incidence of AD and VD. The results of the evaluation insinuated that depression plays a chief role in developing dementia in later stages of life (Barnes, Yaffe, Byers, McCormick, Schaefer, & Whitmer, 2012). Particularly, depression that was developed during the latter half of life can have a major part in AD prodrome, whereas persistent depression can be clinically related to the increased risk of developing VD.

Taylor WD et al. hinted that age-related CVD leads to a successive influence on mood, behaviour, and cognitive function. The authors also emphasized that "vascular depression" might be the ultimate result due to cognitive impairment, and it should be considered as the prime focus of treatment (Taylor, Schultz, Panaite, & Steffens, 2018).

The vascular changes that occur in patients with VD are hypothesized to be the mechanism for the association between depression and dementia. VD and major depressive disorder (MDD) are each associated with an increased risk of developing each other. Besides, significant depressive symptoms can be more noticed in VD than AD.

Diagnosis

The essential feature of VD that aids in clinical diagnosis is impairment in 2 or more cognitive domains. The striking characteristic difference is noted in the following aspects of brain function:

A. Impaired executive function
B. Visuo-constructional impairment
C. Memory and language are relatively preserved

Another factor that clearly distinguishes VD from the other types of dementia is the CVD associated with other focal signs. These traits must be correlated with the findings of neuroimaging to arrive at the final diagnosis. At this juncture, we would also like to highlight the fact that a temporal relationship between abrupt or stepwise cognitive deterioration and cerebrovascular lesions exists, which assists the clinicians in the diagnosing and planning of the treatment.

Clinical Management

The treatment and clinical management of VD primarily aim at eliminating or reducing the severity of the etiologies, such as reduction of obesity, hypertension, hyperlipidaemia, and glucose intolerance. It should also focus on the promotion of dietary and routine exercise strategies right from the beginning of middle age.

Various medications such as cholinesterase, memantine, and cannabis have been tried to treat the disease. However, the effectiveness of cholinesterase inhibitors is still unclear, and it is not used in VD anymore. But during certain instances, they have been tried in cases of mixed forms of dementia.

A study evaluated the efficacy of memantine in patients diagnosed with VD. The results suggested that 20 mg/dl of memantine proved effective in patients with mild to moderate vascular dementia. It also amended the cognitive function steadily through diverse cognitive scales. The patients did not report any signs of deterioration in overall functioning and behaviour. Moreover, the drug did not cause any adverse reactions (Orgogozo, Rigaud, Stöffler, Möbius, & Forette, 2002). Nonetheless, Cannabis extracts (cannabidiol (CBD) and tetrahydrocannabinol (THC)) do not have any clear evidence to support their use for the management of VD (Peprah & McCormack, 2019). Further long-term studies are required to practice the use of this drug for treating VD.

Depression and anxiety may be effectively treated by antidepressants such as selective serotonin reuptake inhibitor (SSRI) and serotonin and norepinephrine reuptake inhibitor (SNRI) (Whittington, Kendall, Fonagy, Cottrell, Cotgrove, & Boddington, 2004). Finally, the importance of sleep hygiene and sleep apnea must not be overlooked during the treatment planning phase and should be re-evaluated if the patient is non-responsive to treatments.

Future trends in research on VD:

Neuroimaging techniques have been used to identify potential biomarkers of cerebral hemodynamics in people with mild to moderate dementia. Currently, there are several treatments that target vascular risk. However, future research must focus on eliminating the etiologies of dementia rather than treating the disease once it manifests. A study revealed that PEA-OXA, which is a compound known to reduce inflammation and oxidative stress, can be used as a therapy for patients with VD (Impellizzeri et al., 2019). Anti-diabetic drugs like metformin that target the GLP-1 receptor could also be used to treat this condition. Moreover, statins and fibrates are known to have anti-inflammatory and antioxidant effects, and they could benefit patients with VD (Sinha, Sun, Kamari, & Bettermann, 2020).

Future treatment perspectives should focus on gene therapy and stem cell therapy. ApoE4 is the gene that is known to cause this disease in the elderly. Individuals with two or more copies of the ApoE4 allele are prone to having a higher risk of developing dementia. However, the risk of this condition is decreased in individuals with one or fewer alleles, especially the ApoE2 (Biffi et al., 2010).

Certain researchers experimented by delivering virus-mediated ApoE gene into mouse model brains. The studies have shown that this therapy has exhibited positive outcomes. Additionally, contemporary developments in stem-cell therapies predominantly focus on regeneration of the neural cell types instead of aiming to replace the injured cells. Frequently applied stem cells are embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), brain-derived neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs). One of these cell types can be transplanted into the human brain to enable regeneration of the lost neurons (Park et al., 2013). Research on stem cell therapy has shown promising results in terms of reversal of spatial memory and learning deficits in animal models. However, human clinical trials are yet to show improved clinical outcomes in mild to moderate cases of dementia. Another preventive approach is by advising vaccines for individuals prone to develop the condition. Vaccination with ACI-35 rouses the host immune response that in turn clears the abnormal Tau protein (Panza et al., 2016).

Conclusion

Vascular changes of the brain can present themselves in several forms, but it is frequently linked to stroke. These vascular changes lead to impairment of cognitive function and eventually result in dementia. However, pure VD seems to be a rare occurrence as it can occur along with other forms of dementia such as AD. There is compelling evidence suggesting that the vascular changes will deteriorate the cognitive function resulting in neurodegenerative changes. Considering the etiologies of various types of dementia, VD seems to be the only type of dementia that can be prevented if timely diagnosis and intervention are made.

References

Attems, J., Jellinger, K., Thal, D.R., & Van Nostrand, W. (2011). Review: sporadic cerebral amyloid angiopathy. Neuropathology and Applied Neurobiology 2011; 37(1):75-93.

Barnes, D.E., Yaffe, K., Byers, A.L., McCormick, M., Schaefer, C. & Whitmer, R.A. (2012). Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Archives of general psychiatry, 69(5), 493-498.

Biffi, A., Plourde, A., Shen, Y., Onofrio, R., Smith, E.E., Frosch, M., et al. (2010). Screening for familial APP mutations in sporadic cerebral amyloid angiopathy. PLoS One, 5(11), p.e13949.

Bir, S.C., Khan, M.W., Javalkar, V., Toledo, E.G., & Kelley, R.E. (2021). Emerging Concepts in Vascular Dementia: A Review. Journal of stroke and cerebrovascular diseases, 30(8), 105864.

Blackman, J.S. (2016). Diagnostic and Statistical Manual of Mental Disorders, by American Psychiatric Association. Washington, DC: Author, 20. Psychoanalysis Psychology, 33(4), 651-63.

Breteler, M.M.B., Van Swieten, J.C., Bots, M.L., Grobbee, D.E., Claus, J.J., Van Den Hout, J.H.W., et al. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology, 44(7), 1246-1246.

Buffon, F., Porcher, R., Hernandez, K., Kurtz, A., Pointeau, S., Vahedi, K., et al. (2006). Cognitive profile in CADASIL. Journal of Neurology, Neurosurgery & Psychiatry, 77(2), 175-180.

Charlton, R.A., Morris, R.G, Nitkunan, A., & Markus, H.S. (2006). The cognitive profiles of CADASIL and sporadic small vessel disease. Neurology, 66(10), 1523-1526.

Cheng, S.T. (2016). Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. Current Psychiatry Reports, 18(9), 1-2.

De Craen, A.J., Gussekloo, J., Vrijsen, B., & Westendorp, R.G. (2005). Meta-analysis of nonsteroidal anti-inflammatory drug use and risk of dementia. American Journal of Epidemiology, 161(2), 114-20.

Esiri, M.M., Wilcock, G.K., & Morris, J.H. (1997). Neuropathological assessment of the lesions of significance in vascular dementia. Journal of Neurology, Neurosurgery and Psychiatry, 63(6), 749-753

Ferri, C.P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., et al. (2005). Global prevalence of dementia: a Delphi consensus study. The Lancet, 366(9503), 2112-2117.
Forette, F., & Boller, F. (1991). Hypertension and the risk of dementia in the elderly. The American Journal of Medicine, 90(3), S14-9.
Hachinski, V.C., Iliff, L.D., Zilhka, E., Du Boulay, G.H., McAllister, V.L., Marshall, J., et al. (1975). Cerebral blood flow in dementia. Archives of Neurology, 32(9), 632-7.
Hachinski, V., Iadecola, C., & Petersen, R.C. (2006). National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke, 37, 2220–2241
Henderson, V.W. (2014). Alzheimer's disease: a review of hormone therapy trials and implications for treatment and prevention after menopause. The Journal of Steroid Biochemistry and Molecular Biology, 142, 99-106.
Impellizzeri, D., Siracusa, R., Cordaro, M., Crupi, R., Peritore, A.F., Gugliandolo, E., et al. (2019). N-Palmitoylethanolamine-oxazoline (PEA-OXA): A new therapeutic strategy to reduce neuroinflammation, oxidative stress associated with vascular dementia in an experimental model of repeated bilateral common carotid arteries occlusion. Neurobiology of Disease, 125, 77-91.
Ishikawa, E., Yanaka, K., Sugimoto, K., Ayuzawa, S., & Nose, T. (2002). Reversible dementia in patients with chronic subdural hematomas. Journal of Neurosurgery, 96(4), 680-683.
Kalaria, R. N., Maestre, G.E., Arizaga, R., Friedland, R. P., Galasko, D., Hall, K., et al. (2008). Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. The Lancet Neurology, 7(9), 812-826.
Knapp, M., Prince, M., Albanese, E., Banerjee, S., Dhanasiri, S., Fernandez, J.L., et al. (2007). Dementia UK. London: Alzheimer's Society, 7.
Khan, A., Kalaria, R.N., Corbett, A., & Ballard, C. (2016). Update on vascular dementia. Journal of Geriatric Psychiatry and Neurology, 29(5), 281-301.
O'Brien, J.T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., et al. (2003). Vascular cognitive impairment. The Lancet Neurology, 2(2), 89-98.
O'Brien, J.T. (2007). Role of imaging techniques in the diagnosis of dementia. The British Journal of Radiology, 80 (special_issue_2), S71-7.
O'Brien, J.T., & Thomas, A. (2015). Vascular dementia. The Lancet, 386(10004), 1698-1706.
Orgogozo, J.M., Rigaud, A.S., Stoffler, A., Mobius, H.J., & Forette, F. (2002). Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke, 33(7), 1834-1839.
Panza, F., Solfrizzi, V., Seripa, D., Imbimbo, B.P., Lozupone, M., Santamato, A., et al. (2016). Tau-based therapeutics for Alzheimer's disease: active and passive immunotherapy. Immunotherapy, 8(9), 1119-1134.
Park, D., Yang, Y.H., Bae, D.K., Lee, S.H., Yang, G., Kyung, J., et al. (2013). Improvement of cognitive function and physical activity of ageing mice by human neural stem cells over-expressing choline acetyltransferase. Neurobiology of Aging, 34(11), 2639-2646.
Peprah, K., & McCormack, S. (2019). Medical cannabis for the treatment of dementia: a review of clinical effectiveness and guidelines.
Peters, N., Opherk, C., Danek, A., Ballard, C., Herzog, J., & Dichgans, M. (2005). The pattern of cognitive performance in CADASIL: a monogenic condition leading to subcortical ischemic vascular dementia. American Journal of Psychiatry, 162(11), 2078-2085.
Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weir, D.R., Ofstedal, M.B., et al. (2007). Prevalence of dementia in the United States: the ageing, demographics, and memory study. Neuroepidemiology, 29(1-2), 125-32.
Poly, T.N., Islam, M.M., Walther, B.A., Yang, H.C., Wu, C.C., Lin, M.C., et al. (2020). Association between use of statin and risk of dementia: a meta-analysis of observational studies. Neuroepidemiology, 54(3), 214-26.
Prince, M., Guerchet, M., & Prina, M. (2013). The global impact of dementia 2013-2050.
Román, G.C., Tatemichi, T.K., Erkinjuntti, T., Cummings, J.L., Masdeu, J.C., Garcia, J.H., et al. (1993). Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology, 43(2), 250.
Sachdev, P., Kalaria, R., O'Brien, J., Skoog, I., Alladi, S., Black, S.E., et al. (2014). Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Disease and Associated Disorders, 28(3), 206.
Schmidt, R., Fazekas, F., Kleinert, G., Offenbacher, H., Gindl, K., Payer, F., et al. (1992). Magnetic resonance imaging signal hyperintensities in the deep and subcortical white matter: a comparative study between stroke patients and normal volunteers. Archives of Neurology, 49(8), 825-827.
Sinha, K., Sun, C., Kamari, R, & Bettermann, K. (2020). Current status and future prospects of pathophysiology-based neuroprotective drugs for the treatment of vascular dementia. Drug discovery today, 25(4), 793-799.
Spitzer, R.L., Williams, J.B., & Gibbon, M.B. (1990). First Structured clinical interview for the DSM-3R, patient edition, American Psychiatric Press, Washington DC.
Taylor, W.D., Schultz, S.K., Panaite, V., & Steffens, D.C. (2018). Perspectives on the management of vascular depression. American Journal of Psychiatry, 175(12), 1169-75.
Tomlinson, B.E., Blessed, G., & Roth, M. (1970). Observations on the brains of demented old people. Journal of the Neurological Sciences, 11(3), 205-42.
Wahlund, L.O., Barkhof, F., Fazekas, F., Bronge, L., Augustin, M., Sjogren, M., et al. (2001). A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke, 32(6), 1318-1322.
Whittington, C.J., Kendall, T., Fonagy, P., Cottrell, D., Cotgrove, A, & Boddington, E. (2004). Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. The Lancet, 363(9418), 1341-1345.
Yamamoto, Y., Craggs, L., Baumann, M., Kalimo, H., & Kalaria, R.N. (2011). Molecular genetics and pathology of hereditary small vessel diseases of the brain. Neuropathology and Applied Neurobiology, 37(1), 94-113.