

Vascular dementia

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ABSTRACT

Vascular dementia (VaD) is a common but heterogeneous condition in which there is a clear temporal relationship between the dementia and vascular disease. It may result from multiple large or small vessel strokes or a single strategic stroke. Subcortical ischaemic VaD includes multiple lacunes and subcortical arteriosclerotic encephalopathy (Binswanger's disease) and imaging shows multiple deep white matter lesions or leukoariosis. Large vessel disease may result in VaD by causing multiple cortical and subcortical strokes, while strategic stroke VaD is caused by a single stroke in a specific area of the brain. On the basis of clinical features and imaging, definite, probable and possible VaD can be defined. Vascular risk factor reduction, particularly the use of antihypertensive agents, remains the most important means to prevent VaD. Treatment is limited although acetylcholinesterase inhibitors may have value. Treating behavioural symptoms may be difficult and newer antipsychotics as well as acetylcholinesterase inhibitor therapy should be considered.

Keywords: Dementia, Vascular

Introduction

Vascular dementia (VaD) is considered to be the second commonest cause of dementia worldwide.¹ It is a heterogeneous condition with multiple definitions. Pierre Marie initially described vascular dementia secondary to subcortical 'état lacunair' and Binswanger identified white matter lesions in demented individuals. Later pathological and clinical studies highlighted the role of cortical damage in multi-infarct dementia.² The definition of VaD must include the presence of dementia with a vascular cause, and a clear temporal relation between the dementia and vascular disease. The heterogeneity results from the different vascular mechanisms and changes in the brain, and ensuing variety of clinical manifestations.³ This overview will briefly cover the epidemiology, pathogenesis, clinical features, risk factors, prevention and treatment of VaD.

Epidemiology

Approximately one-third of individuals over 85 years of age in high-income regions have dementia and about a sixth of them suffer from vascular dementia, resulting in a prevalence of 4-5%.⁴ Very little is known about the epidemiology of dementia in Africa, although Alzheimer's disease is thought to be uncommon.⁵ The anticipated increase in the elderly population and in cardiovascular disease and risk factors in the re-

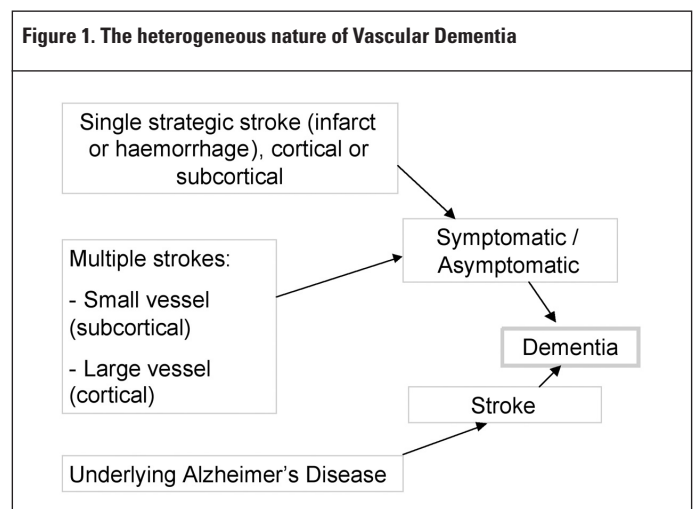
gion will almost certainly effect an increase in VaD in the next few decades. To confirm this we will need validated diagnostic and psychometric tools.⁶

Pathogenesis and Clinical Features

Vascular dementia may result from multiple strokes caused by subcortical small vessel disease or multiple large vessel strokes involving the cortex and white matter. But not all forms of VaD are caused by multiple strokes, and a single strategic stroke may manifest similarly (Fig 1).⁷ Furthermore, a patient with an underlying primary degenerative dementia such as Alzheimer's disease may have one or more strokes and present with features that overlap with VaD.⁸

Subcortical ischaemic VaD is a relatively homogenous grouping that includes two small vessel clinical entities – 'the

Figure 1. The heterogeneous nature of Vascular Dementia

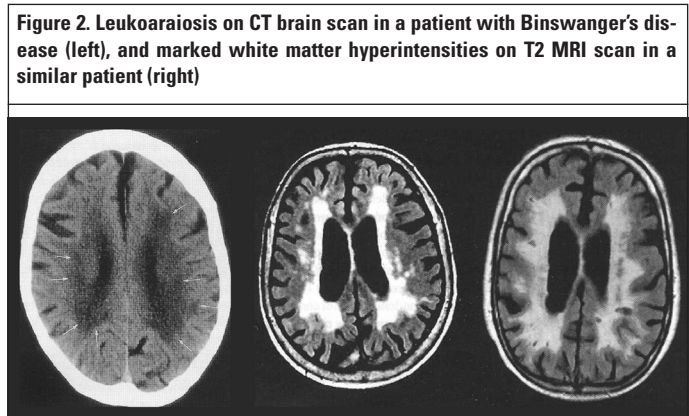


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lacunar state' and 'Binswanger's disease'. It results from either arteriolar occlusion and lacunes (lacunar state) or widespread incomplete infarction of white matter due to critical stenosis of medullary arterioles and hypoperfusion (subcortical arteriosclerotic encephalopathy or Binswanger's disease).¹ Clinical features include progressive or stepwise development of motor and cognitive executive slowing, memory deficits, dysarthria, mood changes, urinary symptoms, and extrapyramidal features with gait disturbance (lower-body parkinsonism).⁹ These manifestations probably result from ischaemic interruption of parallel circuits from the prefrontal cortex to the basal ganglia and corresponding thalamocortical connections.¹ Focal neurological signs occur in both conditions. Whether these two small vessel entities are all part of one condition or distinctly separate has been debated for decades.¹⁰

Brain imaging (CT or MRI) showing deep white matter lesions is essential for the correct diagnosis of subcortical ischaemic VaD (Fig 2). Unfortunately the understanding of VaD is further complicated by the use of the term leukoaraiosis to describe these periventricular white matter lesions. Leukoaraiosis was first used by Hachinski et al in 1987.¹¹ It was derived from the Greek roots 'leuko' (white) and 'araiosis' (rarefied) to provide a purely descriptive term that in the absence of knowledge on what exactly caused these appearances, could be used in place of any other labels that implied a knowledge of their pathogenesis.



Although leukoaraiosis is thought to be caused by ischaemic demyelination, most often the result of arteriosclerosis, a similar appearance is seen in many other conditions including: vasculitis, multiple sclerosis, acute demyelinating encephalomyelitis, post-traumatic, leukodystrophy, HIV encephalopathy, CADASIL (cerebral autosomal dominant angiopathy with subcortical infarcts and leukoencephalopathy), vitamin B12 deficiency, and other infective and toxic causes of demyelination.¹⁰ The radiological picture may also occur in people without dementia as a normal to the wall of the lateral ventricles (caps and rims) correspond to primary gliosis secondary to leakage of CSF through an aging ependymal wall.¹⁰

Large vessel disease may result in VaD by causing multiple strokes in cortical and subcortical areas. Clinical features will typically be of a stepwise progression of dementia with associated focal neurological signs.

Strategic stroke VaD is caused by a single stroke in a specific area of the brain. Most often these are large vessel strokes, but small vessel strokes involving particularly the thalamus may have the same result.⁷ For example, large anterior cere-

bral artery strokes may present with combinations of abulia, transcortical motor aphasia, memory impairment, dyspraxia, amnesia, apathy and other behavioural changes. Non-dominant hemisphere right middle cerebral artery occlusions may present with psychosis and behavioural decline and a posterior cerebral artery infarct may present with an amnesic syndrome (thalamoperforating branches), psychomotor agitation, visual hallucinations and other visual disturbances.⁹

Diagnostic Criteria

The National Institute of Neurological Disorders and Stroke, and the French Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria¹² for the diagnosis of VaD combine key clinical and radiological criteria (Table 1). The dementia syndrome should develop within three months of the vascular event. While the timespan is arbitrary it helps to avoid misclassification of a patient with a dementia who develops a stroke years later. Of course it is not helpful when the vascular event is 'silent' or there is a progressive dementia with widespread white matter disease on imaging.⁹

On imaging, large vessel lesions should be in the dominant hemisphere or both hemispheres. It is believed, though not proved, that cognitive deficits in dementia should be attributed mostly to the dominant hemisphere.⁹

On the basis of clinical features and imaging, definite, probable and possible VaD can be defined. Definite VaD requires all the criteria with no more than 3 months between the stroke and the dementia, and confirmatory pathology. Probable VaD requires the same but without pathology, and possible VaD is diagnosed in the absence of radiology, pathology and a clear temporal relationship.

Table 1. The NINDS-AIREN criteria for the diagnosis of Vascular Dementia¹²

Require both clinical and radiological criteria (severity and topographical):
A. Clinical
a) Dementia
b) Cerebrovascular disease
c) Temporal relationship between (i) and (ii), with evidence of cerebrovascular disease first
B. Radiological
a) Topography
i. Large vessel stroke in
1. bilateral anterior cerebral artery territory, or
2. posterior cerebral artery territory, or
3. association areas (parieto-temporal, temporo-occipital including angular gyrus), or
4. border zone carotid territories
ii. Small vessel disease
1. extensive periventricular white matter lesions, or
2. lacunes in basal ganglia or frontal white matter, or
3. bilateral thalamic lacunes
b) Severity
i. Large vessel stroke: large vessel territory lesions of the dominant hemisphere, or bilateral large hemispheric strokes
ii. Small vessel disease: white matter lesions involving at least 25% of the total cerebral white matter

Risk factors for VaD

These are not surprisingly the usual vascular risk factors, with the most important being hypertension. However, other specific factors which increase the risk of dementia include: left (dominant) hemisphere strokes (not explained by dysphasia alone), lower blood pressure, orthostatic hypertension¹³ and larger periventricular white matter ischaemic lesions on MRI.¹⁴

Prevention of VaD

Prevention strategies should focus on reduction of stroke and cardiovascular disease risk factors. Few studies of risk factor reduction have specifically focused on VaD as an outcome. In a large population based study from Rotterdam, participants who were already on blood pressure lowering agents had a relative risk of 0.3 (95% CI 0.1 to 0.9) compared to those not on blood pressure lowering agents, irrespective of possible confounding factors such as diastolic and systolic blood pressure, diabetes, previous stroke, body-mass-index, smoking and atherosclerosis.¹⁵ In patients who have had a stroke or transient ischaemic attack (TIA), the addition of perindopril with or without indapamide in the PROGRESS study resulted in a relative risk reduction of 12% (95% CI, -8% to 28%) for the development of dementia as defined by DSM IV. Cognitive decline (defined as a reduction of ≥ 3 points on the mini-mental status examination) was reduced by 19% (95% CI, 21 to 61%). More significant reduction in cognitive decline or dementia was seen in the patients who actually had a recurrent stroke than in those who did not.¹⁶

Treatment of VaD

The treatment of VaD includes the basic care of any patient with dementia and control of vascular risk factors to prevent progression. The role of aspirin is not clear. In a small randomised controlled trial (RCT), a dose of 325mg daily was found to stabilise cognition,¹⁷ but this has not been confirmed by larger studies.¹⁸

Some authors have suggested a synergistic interaction between major causative factors in Alzheimer's dementia (amyloid) and VaD (vascular insufficiency) and recommended the use of acetylcholinesterase inhibitors in VaD.¹⁹ Cholinergic drugs are likely to be effective in VaD because these patients have cholinergic deficits related to ischaemic involvement of basal forebrain neurons (nucleus basalis of Meynert) or their projections.²⁰ A RCT showed beneficial effects of galantamine (24 mg daily) on cognition, global function, functional abilities and behavioural symptoms in patients with probable VaD.²¹ These findings are derived from a post-hoc subgroup analysis and must be confirmed in further trials. In a recent randomised controlled study of donepezil (5mg or 10mg versus placebo) in 603 patients with VaD, patients given donepezil showed improvement in cognition and global function at 24 weeks.²²

The Cochrane Library of systematic reviews does not provide support for the use of piracetam in dementia,²³ but does provide some early evidence that memantine,²⁴ ginkgo bilboa²⁵ and cytidinephosphocholine²⁶ are promising agents that require further investigation.

Treatment of Behavioural Symptoms

Behavioural symptoms are a problem in some people with VaD and may be difficult to treat. A ten year prospective follow-up study of 99 patients with VaD living with a carer in

Oxfordshire, United Kingdom, underwent four monthly follow up with assessment of patients and interview of the carers.²⁷ Verbal aggression is the most common and longest lasting form of aggressive behaviour. Aggressive resistance and physical aggression are most likely to persist until death and intimate care is the commonest precipitating factor for this behaviour. The investigators found no correlation with age, gender or time since onset of dementia, although physical aggression was most prevalent in people with severe dementia.

Haloperidol is useful for aggression in patients with dementia, but at the expense of marked side effects.²⁸ There is no evidence to support the use of thioridazine in dementia.²⁹ Risperidone used at a mean dose of 0.95mg daily significantly improved behavioural symptoms in a RCT of 345 patients against placebo,³⁰ and in another RCT of 344 patients showed a non-significant trend towards better control of behavioural symptoms than haloperidol with fewer side effects.³¹

Conclusion

Vascular dementia is a common but confusing disorder. The pathogenesis for the most part is incompletely understood, and the treatment unsatisfactory. While we wait for nosological, pathological and subgroup specific treatment guidelines, we need to stick to the standard diagnostic guidelines, use sensible evidence based therapies and prevention, and above all care for the overall well-being of the dementia patient and their carers.

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Commentary

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Dementia is an extremely common problem in the developed world where the elderly population is well cared for and survive into extreme old age. The population of the elderly old is slowly increasing and it is not uncommon for survival to reach the 90's and above. In the developing world where nutrition, medical care and many other risk factors for longevity are perhaps not as advanced, the average age of the elderly is much younger. An overall estimation of the prevalence of Vascular dementia is given at up to 13% of all dementia.¹ Dr. Connor points out that population studies of dementia, its subtypes and specifically vascular dementia are lacking in the developing world and in particular there are no reliable statistics in South Africa. It is thought, in some circles, that even Alzheimer's disease is less prevalent in South Africa. This is yet to be proven by in depth epidemiological studies, taking the social norms and customs into account. Dementia is defined by a social parameter of functionality and this may well differ even within the ethnic groups of South Africa. Dr. Connor so rightly notes that the accepted diagnostic psychometric tools have not been adequately tested in vascular dementia and this is the case for dementia as a group, amongst the various ethnic groups of the developing world. I could not find any study validating the mini mental status exam for the black ethnic group in South Africa.² It remains to be studied and proven, and it is my personal bias that with adequate evaluation and testing the incidence and prevalence of dementia and all its subtypes will not be very different in the developing world as compared to the developed world; if indeed the average survival age of the population, risk factors and social norms are adequately controlled for. As noted, however, by Dr. Connor there may well be a bias to a higher incidence of vascular dementia in the black ethnic groups in South Africa where uncontrolled hypertension, hemorrhagic, embolic, lacunar, and Binswanger complications of hypertension are likely to be more prevalent than the amyloid angiopathy seen in the developed world.³


Seventy percent of dementia can be ascribed to abnormalities of protein metabolism; specifically 3 proteins, beta-amyloid, alpha-synuclein and tau protein.³ Alzheimer's disease is the most complex, being associated with an abnormal accumulation of beta-amyloid protein but also alpha-synuclein and a degree of tau protein. Lewy body disease, Parkinson's dis-

ease, and multisystem atrophy all have abnormal accumulation of alpha-synuclein and all have an accompanying dementia. Similarly, frontotemporal dementia, corticobasal dementia and progressive supranuclear palsy are associated with abnormal accumulations of tau protein. Vascular dementia is more common than these other neurodegenerative causes of dementia but is significantly less common than Alzheimer's disease. Dr. Connor might however have stressed the diagnostic implications when imaging studies, and particularly MRI, demonstrate Binswanger changes in a patient clinically diagnosed with Alzheimer's disease. The frequency of mixed Alzheimer's and vascular dementia is high and is perhaps more common than pure Vascular dementia alone. The clinical implications are those of a possibly more rapidly progressive dementia along with the added risk for stroke, and other complications of possible hypertension. The management implications are that of a more difficult behavior profile with more aggressive and belligerent behavior.

The characteristic behaviors of patients with vascular dementia as mentioned by Dr. Connor often include a more verbally aggressive profile than that seen with Alzheimer's disease. The hallmark of the vascular dementia patient however, especially noted as they reach end stage, is a remarkable preservation of personality; the vascular dementia patient still knows how to "press buttons" almost to the end. The Alzheimer patients however, are much more docile and compliant with a remarkable behavioral uniformity towards the end stages. In managing these behaviors Dr. Connor did not discuss the use of behavioral intervention that, even in the more difficult vascular dementias, is still far preferable than medication; medication inevitably increases sedation and is associated with an increased incidence of falls and other complications such as aspiration pneumonia. The use of the newer, less sedating, antipsychotics such as olanzapine and for sleep disturbances, trazadone can be most helpful in managing these behaviors.

Dr Connor has however provided us with an excellent and up to date overview of Vascular dementia with all the evidence based data available on the subject.

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