

Dementia And Vascular Disease

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Introduction

In the Western world, vascular disease is thought to be the second most common cause of dementia, following Alzheimer's disease.¹ Vascular disease is at least partially preventable and treatable, so increasing awareness of this association may decrease the incidence of dementia. This paper will discuss the controversies about vascular disease and dementia, while stating the known facts on which doctors can base clinical decisions. Vascular disease may lead to subtle cognitive changes, which in turn could be a warning sign of impending dementia. This provides the clinician the opportunity to identify individuals at risk and to institute preventive measures.

In the United States, about 500,000 people suffer from a stroke each year and stroke is the third leading cause of death. It has long been known that cognitive deficits may result from a stroke, yet only recently have studies shown that dementia occurs in approximately one-fourth to one-third of stroke cases.² The prevalence of all forms of dementia, including vascular dementia, increases with age. In Europe, the prevalence of vascular dementia is estimated to be 1.5-4.8% for individuals between the ages of 70 and 80 years old.³

At the end of the 19th century, Otto Binswanger and Alois Alzheimer studied the relation between vascular pathology and reduced cognitive abilities. However, 70 years later, Tomlison and Blessed completed a more systematic study showing a relationship of vascular pathology to dementia. In 1974, Hachinski coined the term *multi-infarct dementia* (MID) to emphasize that the dementia is attributable to small and/or large cerebral vessel infarctions. Later, researchers used the term *vascular dementia* (VaD), which is a more encompassing term and encourages doctors to consider various vascular pathologies, including hemorrhage, which may lead to dementia. Most recently, authors propose the term *vascular cognitive impairment* (VCI) with the intent of broadening the concept even further: vascular disease may produce a range of cognitive deficits from mild to severe, and early recognition of a deficit allows the clinician to intervene before the dementia occurs.

First, this paper will present an illustrative case of vascular-induced dementia. Then, we will review the risk factors for vascular disease and dementia, with particular emphasis

on the interaction of vascular and degenerative disease processes. The clinical profile of vascular dementia will be described. The important pathologic findings will be discussed, with exploration of the possible underlying pathogenic mechanisms: we hope to demonstrate the many ways in which vascular disease can lead to dementia, and we will present the controversial findings of white matter lesions and their possible role in dementia. Finally, we will propose a framework for the management of vascular cognitive impairment.

Case

A 68 year-old right-handed teacher was in good prior health when she was suddenly found to be confused. She was admitted to hospital obtunded and remained somnolent for the first ten days. The only past history was that of borderline diabetes mellitus, and she had no history of hypertension or smoking. On examination, the patient had a supranuclear vertical gaze palsy. A CT scan of the brain performed ten days after admission showed enhancing bilateral medial thalamic infarctions.

The patient was discharged and lived in her home with constant care because of severe memory impairment. The family noted a personality change in that she was less inhibited. Over the next five years, she was seen for follow-up in the neurology clinic and underwent sequential neuropsychological testing. Her memory remained stable over time.

Five years after the stroke, she underwent a brain MRI, which confirmed the bilateral thalamic infarcts and no other lesion (Figure 1). Her last neuropsychological testing revealed a stable pattern of amnesia.

Risk Factors

The risk factors for vascular disease are well established, however, little is known about the risk factors for vascular dementia. Traditionally, the latter have been directly extrapolated from the vascular disease literature and may thus

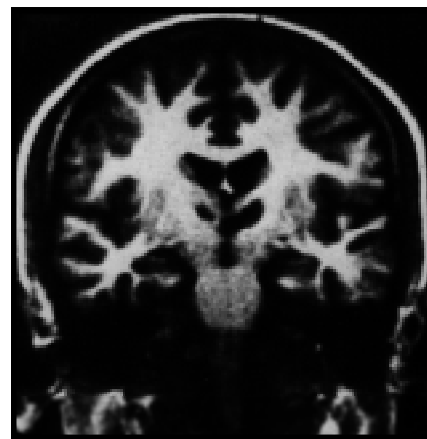


Figure 1. MRI showing bilateral thalamic infarctions.

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Table 1. Risk Factors For Vascular Dementia

Non-reversible risk factors

- Increasing age*
- Genetic predisposition (eg. CADASIL)
- Geographic origin (eg. African-American, Asian)
- Prior strokes (particularly if large, multiple, or in vulnerable locations)
- Low education level

Reversible risk factors

- Hypertension
- Coronary artery disease
- Atrial fibrillation
- Diabetes mellitus
- Hyperlipidemia
- Hyperglycemia
- Smoking

*Only well established risk factor

be classified into two categories: non-reversible and reversible risk factors (Table 1).

Increasing age is the only well established risk factor for vascular dementia.⁵ The gender status as a risk factor has been controversial, and a recent study found men and women to be equally affected. As the race to complete the human genome project is on, it is becoming more obvious how genetics plays an ever increasing role in our understanding of disease processes, and the field of vascular dementia is no exception to this observation. For instance, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic disease that involves Notch3 mutations, leading to the presence of subcortical infarcts and dementia in 90% of affected persons who died with the condition.⁶ As disorders such as CADASIL are being defined, clinicians may one day be able to predict who will develop vascular cognitive impairment and thus better target our therapy at high-risk individuals.

A history of prior stroke is an important risk factor for vascular dementia. Not only is the size and number of infarcts relevant, but also the location of even a single strategically placed lesion may be sufficient to cause dementia. Prevention of further stroke with appropriate medical or surgical therapy is crucial, as evidence of a prior ischemic stroke on brain imaging has been associated with a nine-fold increase in the development of dementia.²

Vascular Disease And Alzheimer's Disease

In a study of pathologically proven cases of AD, the prevalence and severity of dementia was increased in cases with cerebral infarcts as compared to those without infarction.⁷ Several factors may play a role in the interaction of these two disease processes, leading ultimately to cognitive

impairment. On the one hand, the two processes may share common risk factors. Hypertension, diabetes mellitus, and smoking have been associated with vascular disease but also with AD. Furthermore, ApoE4 appears to increase the risk not only for the development of AD but also for that of dementia in stroke patients.⁸ Finally, hyperhomocysteinemia, a well-documented vascular risk factor, is also found to be associated with AD. On the other hand, vascular and degenerative pathology may interact to lead to cognitive decline. Atherosclerosis is increased in both conditions.⁹ Amyloid deposits may occur in certain conditions associated with vascular disease (eg. Hereditary Cerebral Hemorrhage with Amyloidosis) but also play a pivotal role in the pathogenesis of AD. Further study is required to clarify the mechanisms whereby vascular and degenerative processes interact.

Clinical Presentation

Although several sets of diagnostic criteria have been published for vascular dementia,^{10,11} this entity remains under-recognized and the full spectrum of the cognitive impairment largely underexplored. This may be explained, at least in part, by the variable presentation of vascular dementia and vascular cognitive impairment, dependent on the nature, the location, and extent of the causative lesion(s). Furthermore, these cases are most often not under the care of dementia specialists, but rather are cared for by physicians who concentrate on the cause and treatment of the stroke. In fact, when specifically addressed, the frequency of dementia in a hospitalized cohort of 251 patients admitted with stroke was found to be as high as 26%.²

As when faced with any patient with cognitive inefficiencies, the history should be obtained from not only the patients themselves, but also from the caregivers. Characteristic historical features are a sudden onset of neurological deficits, a stepwise deterioration, and a fluctuating course.¹² Each of these three features is present in over 90% of cases, and help differentiate these patients from persons with AD. Also, over 90% of vascular dementia cases have a history of prior stroke and three-fourths of cases have a complaint of focal neurological symptoms. Finally, clinicians should inquire into possible confounding factors, such as incriminating medications, active medical problems, and psychiatric illness. Psychiatric evaluation is important to obtain in patients with vascular dementia, because depression is found in up to one-fifth of cases and can be successfully treated with appropriate antidepressants.

On examination, focal neurological signs, such as unilateral weakness, sensory loss, asymmetric reflexes, or a Babinski sign, are found in over 85% of cases. Other neurological signs may include primitive reflexes, homonymous hemianopsia, pseudobulbar palsy, or a gait disorder. The cardiovascular examination is crucial in patients

with suspected vascular dementia, as the identification of specific treatable causes, such as hypertension, atrial fibrillation, or a carotid bruit, will help direct therapy appropriately.

Various factors on the history and physical examination of patients with suspected vascular disease resulting in dementia appear to be characteristic enough that an “ischemic score” has been devised to help differentiate these patients from individuals with Alzheimer’s disease.¹³ The original score assesses for the presence of thirteen clinical

Table 2. Ischemic score (modified from reference #13)	
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
Associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2
Maximal score	18
Vascular range	7-18
Mixed range	5-6
Degenerative range	0-4

features and attributes a score out of 18 (Table 2): if the score is above 7, it suggests a diagnosis of multi-infarct dementia (MID) and if below 4, it suggests AD. This score has since been validated and a recent meta-analysis of pathologically confirmed MID and AD cases has been performed.¹⁴ The authors of this meta-analysis found that the original cutoff scores allowed for correct identification of MID and AD cases in 84% and 76%

of cases, respectively. Furthermore, a score of 7 or above allowed for 89% sensitivity and 89% specificity for the diagnosis of MID. Despite the proven validity of this score, several items appear less discriminating and other authors have suggested revised ischemic scores, also with additional items assessing for neuroimaging.

All diagnostic criteria thus far proposed^{10,11,13,15,16} have proven valuable in identifying cases with a vascular component to the dementia, however are not good at excluding a degenerative component, such as AD. Quite often, there is a “mixed cause” of dementia. Even if a stroke component is recognized but exclusion of a degenerative component is difficult, it is still important to proceed with the recognition of specific stroke risk factors, which should be aggressively treated.

Pathology And Pathophysiology

No gold standard for the diagnosis of vascular dementia is available. The attribution of cognitive changes to vascular pathology is an area of controversy: the likelihood that the vascular pathology, and not some other disease process, is responsible for all, the majority, or a part of the observed clinical changes is, at best, only an estimate.

Table 3. Pathological Findings In Vascular Dementia

Macroscopy

Atrophy (cortical and/or subcortical)
 Ventricular dilatation
 Infarcts (usually in large vessel territories, multiple, and of various ages and sizes -may see lacunes)
 Hemorrhages
 White matter abnormalities
 Vessel abnormalities (thrombotic plaques, arteriosclerosis)

Microscopy

Infarcts (acute, subacute, chronic)
 Cortical granular atrophy
 Laminar necrosis
 Diffuse white matter spongiosis
 Periventricular myelin loss
 Vessel abnormalities (atherosclerosis with subintimal hyperplasia and lipohyalinosis; occlusion; amyloid or non-amyloid deposits in vessel wall)
 Etat criblé
 Senile plaques and/or neurofibrillary tangles

The pathology of vascular disease and cognitive changes has been reviewed elsewhere.¹⁷ Various macroscopic and microscopic changes are observed (Table 3). In regards to cerebral infarction and dementia, several studies have shown that the location of the pathology tends to be bilateral and involve large vessel (middle cerebral artery and posterior cerebral artery) territories. Other studies have demonstrated the presence of lacunes in the brains of these patients, either placed in multiple locations, or in a single strategic area of the brain. For example, detailed clinico-anatomical correlations¹⁸ have identified that lesions of specific regions within the thalamus — in particular, the anterolateral and the medial thalamus — are associated with severe neuropsychological deficiencies. Other strategic locations include the frontal white matter or base of the forebrain, basal ganglia, genu of the internal capsule, hippocampus, mamillary bodies, and the midbrain and pons.

On microscopic analysis, Alzheimer-type changes (neurofibrillary tangles and senile plaques) may be present and complicate the picture. The term “mixed dementia” is used when both vascular and degenerative changes are felt to have contributed to the cognitive decline.

The pathophysiologic mechanisms whereby vascular pathology leads to the causation of cognitive impairment remains elusive. This may be explained in part by the fact that many different vascular pathologies may lead to cognitive impairment, including cerebral thrombosis, cardiac embolism, and hemorrhage. We will discuss one of the more well-understood mechanisms — ischemia — and then address another important, although controversial, mechanism, i.e. the role of white matter abnormalities in the causation of cognitive deficits.

The most accepted mechanism of vascular dementia involves the implication of an ischemic process, either via an hypoxic, hypoperfusive, and/or an occlusive mechanism. Chronic hypertension is associated with several pathologies which may lead to cerebral infarction and cognitive deficits. Hypertension causes a shift in the cerebral blood flow (CBF) autoregulation curve to the right: thus, a relative decrease in the blood pressure, due to a hypotensive episode for example, is likely to lead to a greater than expected decrease in CBF in the watershed zones (hypoperfusion problem). Furthermore, hypertension is associated with arteriosclerosis, which is known to be increased in cases with vascular dementia, and leads to narrowing of the cerebral luminal vasculature (occlusion problem). Finally, other disorders such as pulmonary diseases or blood diseases (e.g. sickle cell anemia) may cause a hypoxic injury to the brain (hypoxia problem).

White Matter Lesions

The role of white matter abnormalities in the causation of cognitive dysfunction is less well established. A recent review of white matter pathology in 40 cases with vascular dementia revealed: 1) focal pathology including large and small infarctions in the white matter; and 2) diffuse white matter pathology involving perifocal rarefaction surrounding infarcts and white matter lesions without infarcts.¹⁹

Although initially described almost a century ago, the acceptance of Binswanger's disease as a clinical entity remains controversial. Nevertheless, recent papers argue that modern day research corroborates the existence of such a disease process²⁰ and diagnostic criteria have been published. Several pathogenic mechanisms appear implicated in the causation the deep white matter changes of Binswanger's disease, and hypoxia-ischemia resulting from watershed injury seems to play a key role. Vessel changes, such as arteriolosclerosis, and widening of the extra-vascular spaces (*état criblé*) have been observed. These pathologic changes appear to result in the clinical syndrome of a parkinsonian gait, incontinence, pseudobulbar palsy, and executive dysfunction. Brain imaging shows periventricular white matter changes called *leuko-araiosis*, referring to rarefaction of the white matter. However, this imaging abnormality is non-specific, as it may be found in normal age-matched controls, as well as in patients with disease processes such as AD and normal pressure hydrocephalus.

Thus, what is the significance of leuko-araiosis (LA)? The estimate of the prevalence of this finding is variable, depending on the population of study (community vs. hospitalized cases, elderly vs. younger cases, etc.) and on imaging technique used. Several risk factors for the presence of LA have been found. Undisputedly, age and hypertension are associated with LA. Indeed, the prevalence of LA in individuals over the age of 65 years old has

been quoted to be as high as 100%. Other risk factors, such as diabetes mellitus, smoking, cardiac arrhythmia, hyperlipidemia, and ApoE status remain controversial. Pathological correlates of LA include a decreased density of glial cells, diffuse vacuolation, and sparing of the subcortical U-fibers.²¹ The pathophysiologic mechanism whereby these lesions occur is postulated to be secondary to hypertensive vascular injury to deep penetrating vessels supplying the white matter, vessels which are known to have poor collaterals. This leads to recurrent and "slow" ischemia of the white matter, resulting in the observation of LA on imaging. The clinical relevance of LA — as to whether LA is associated with cognitive impairment or not — remains controversial. Although a recent study of elderly subjects did find such a correlation,²² this is currently being assessed with more rigorous methodology.

Management

Prognosis for patients with vascular dementia is worse than that for AD patients: the three year mortality rate in cases over the age of 85 years old, is quoted at 67%, as compared to 42% in AD, and 23% in non-demented individuals.²³ However, outcome is ultimately dependent on the underlying risk factors and mechanism of disease, and further studies taking these distinctions into account are warranted.

Management of cases at risk for, or with established vascular cognitive impairment, may target various levels, depending on the patient's medical background and where the patient is at in the course of the disease. Chui recently proposed²⁴ an integrated classification of vascular brain injury based on treatment strategy (Table 4). For each case, the clinician should focus systematically on specific treatment strategies, addressing in turn primary prevention (risk factors), secondary prevention (mechanistic cause of vascular injury), and, if applicable, tertiary amelioration (in cases with functional impairment). Also, this classification emphasizes the need for early detection of patients with minimal cognitive impairment who are at risk for developing a dementing illness: these patients could then benefit from aggressive and early treatment.

It is beyond the scope of this paper to discuss management of each factor listed in Table 4, which warrant non-pharmacologic, medical, and/or surgical treatments. However, we will mention a few recent studies on medical management in vascular dementia. Several studies present the benefit of xanthine derivatives, such as pentoxifylline, which is thought to alter red blood cell and platelet properties and propentofylline, which works as a glial cell modulator. Other studies show benefit from agents such as posatirelin, a synthetic peptide with monoaminergic and cholinergic effects. The flaw of these papers is attributable to grouping all cases with vascular disease and dementia

Table 4. Management (modified from reference #24)

Risk factor modification (Primary prevention)

Hypertension
Hyperlipidemia
Atrial fibrillation
Smoking

Treatment of underlying mechanism (Secondary prevention)

Ischemia
 Acute: atherosclerosis, cardioembolism, vasculitis
 Chronic: atherosclerosis, CADASIL
Hemorrhage
 Hypertension
 Vascular malformation: AVM, aneurysm
 Cerebral amyloid angiopathy: sporadic, hereditary

Treatment of established symptoms (Tertiary amelioration)

Cognitive: amnesia, aphasia, neglect
Behavioral: disinhibition, aggression
Psychiatric: depression, anxiety, apathy
Neurological: weakness, visual disturbance

CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

AVM: arteriovenous malformation

into a single group, regardless of the underlying presumed pathophysiology. At this point in time, no therapy for vascular dementia is FDA approved in the US.

Conclusion

This article presents the current understanding of cognitive impairment in patients with vascular disease, with an emphasis on the probable interaction of vascular and degenerative processes. Management aims at primary prevention, secondary prevention, and tertiary amelioration. Further study in this field is underway, and other treatment options will become available.

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