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VASCULAR DEMENTIA

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If psychiatrists were asked to list the major advances of the last 20 years in their specialty, the molecular biology of dementia would figure prominently. Yet, in the face of rapid progress in understanding the molecular pathogenesis of Alzheimer's disease, the biology of vascular dementia remains poorly understood. Haschinski[1] argues that vascular dementia is the single most preventable and potentially treatable cause of dementia in late life. His views contrast with the public pessimism and therapeutic nihilism frequently encountered in the care of dementia sufferers. This review summarises the causes, clinical features and opportunities for prevention and treatment of vascular dementia. Emphasis is placed on the need for skilful diagnostic appraisal of early cognitive impairment in late life.

CAUSES OF DEMENTIA

In 1968, a Ciba symposium[2] led to a radical rethink of the causes of dementia. The historical pre-eminence of cerebrovascular disease was by then well established in the public mind as the most frequent cause of dementia in late life. 'Hardening of the arteries of the brain' was assumed by physician and layman alike to be the commonest cause of cognitive decline in old age. For much of the present century, Alzheimer's disease was believed to be a rare cause of pre-senile dementia and little was taught about it in medical schools. The Newcastle group of Tomlinson, Blessed and Roth[3] revolutionised thinking on the causes and courses of senile dementia, and established the importance of Alzheimer's disease in the community. Neurochemical studies soon followed and the discovery in Edinburgh[4] of the cholinergic deficit in Alzheimer's disease, and its potential reversibility - in a manner akin to L-Dopa replacement therapy in Parkinson's disease. These findings promoted massive collaborative international efforts to understand Alzheimer's disease and so to address one of the major health problems of the age. Molecular biological studies of Alzheimer's disease now reveal that at least five genes contribute to early-onset familial Alzheimer's disease and three others are important in late-onset Alzheimer's disease. The position regarding inheritance with vascular dementia remains poorly understood. Neuropathologists recognise several distinct pathological processes that could produce disease of the cerebral vasculature (Table 1), and this diagnostic heterogeneity has confounded the study of 'vascular dementia' often considered as a single entity. Added to this was uncertainty about the clinical diagnosis of vascular dementia, especially when made in old age which made neuropathologists suspicious that vascular dementia was often overdiagnosed.[5]

New accurate methods to estimate cerebral blood flow in human subjects combined with improved methods to detect structural brain abnormalities are insufficiently used to investigate old people. Epidemiological studies based solely on clinical data are therefore unreliable: the most informative surveys are based on postmortem diagnoses, and of these key studies are summarised on Table 2. Importantly, the methods used in studies cited in Table 2 are not comparable. Corsellis[6] did not include dementias other

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TABLE 1
Causes of vascular dementia.

	subtype	*pathological features*
Common	Multi-infarct dementia	Bilateral cortical infarcts
	Single infarct dementia	Lesions of angular gyrus or intralaminar thalamic nuclei
	Mixed dementia	Vascular and Alzheimer features co-exist
Uncommon		
	Binswanger's disease	Diffuse demyelination of subcortal white matter and lacunar infarcts
	Cerebral vasculitis	Inflammatory change in small vessels
	CADASIL	Scattered cortical infarcts
	MELAS	
	Syphilis	Periarteritis and endarteritis with fibroblastic proliferation and necrosis/occasional gumma
	AIDS	
	Cerebral DLE/PAN	Focal cranial arteritis
	Cranial arteritis	Subacute inflammation

Abbreviations: CADASIL: cerebral autosomal dominant arteriopathy with stroke-like episodes and leucoencephalopathy; MELAS:mitochondrial encephalopathy with lactic acidosis and stroke; AIDS: aquired immune deficiency syndrome; DLE: disseminated lupus erythematosus; PAN: polyarteritis nodosa.

TABLE 2
Relative frequency of vascular dementia in autopsy series.

Report	N	Alzheimer dementia	Incidence (%) of vascular dementia	Mixed dementia
Corsellis (1962)[6]	89	30 (34%)	42 (47%)	17 (19%)
Sourander & Sjögren (1970)[7]	258	132(51%)	72 (28%)	-
Tomlinson *et al* (1970)[3]	50	25 (50%)	9 (18%)	9 (18%)
Todorov *et al* (1975)[8]	675	206 (31%)	123 (18%)	241 (36%)
Molsa *et al* (1985)[9]	58	28 (48%)	11 (19%)	6 (10%)
Wade *et al* (1987)[10]	65	38 (58%)	10 (5%)	6 (9%)

than those with features of Alzheimer's disease or cerebrovascular disease; Sourander and Sjögren[7] did not include a mixed category and others have found the criteria of Todorov[8] difficult to replicate. The remaining papers place the incidence of vascular dementia in developed Western societies between 15% and 19% of all dementias in old age. Caveats abound, however, and it would not be surprising to discover important large variations attributable to racial and socioeconomic differences between populations much as are reported for cerebrovascular disease within Scotland.[11]

Clinical and pathological criteria that should form the basis of a diagnosis of vascular dementia are poorly established. The work of the Newcastle group[3] pioneered careful correlative clinicopathological studies and suggested as a useful criterion that the total volume of infarcted or softened brain tissue must exceed 50 ml to cause vascular dementia. Exceptions to this were quickly noted: in hypertensive cerebrovascular

disease, the volume of lacunar infarcts may be much less than 50 ml but dementia may be evident clinically. Thus in vascular dementia both the volume and the distribution of brain lesions are important determinants: especially important is damage to structures for which the brain has no satisfactory alternative ('bottleneck structures') and which are critical to memory. The term 'multi-infarct dementia' is sometimes wrongly used as being synonymous with 'vascular dementia' but there are important differences between these two conditions. Multi-infarct dementia is attributed to multiple large bilateral cortical cerebral infarcts, whereas vascular dementia is a wider term embracing multi-infarct dementia together with all other causes of cerebrovascular disease that lead to cognitive impairment.

Clinical features

Modern diagnostic systems support a clinical diagnosis of probable vascular dementia when there is a combination of neuropsychological evidence of a dementia and neurological signs consistent with stroke. Importantly, chronological precedence of the stroke over the dementia is central to most diagnostic reasoning. From a clinical and practical standpoint, the need to identify clear evidence of a stroke leads to failure to recognise some forms of vascular dementia especially those which are uncommon. It is more helpful, particularly when planning patient care and possible treatments, to identify risk factors for vascular dementia, the clinical features listed below and the results of brain imaging, especially single proton emission computed tomography (SPECT). Undue reliance on the detection of an earlier stroke can sometimes be unhelpful.

The clinical features of vascular dementia are encapsulated in the Haschinski Ischaemic score.[12] Although widely used, this score does not possess high validity and reliability but its content is a useful clinical *aide memoire*. The items in it were selected from contemporary psychiatry textbooks and summarise the clinical features of vascular dementia attributable to ischaemic vascular disease. These are sudden onset (usually following stroke), step-wise deterioration; relative preservation of personality and insight; depressive symptoms; emotional lability and episodes of prolonged crying or laughter. Nocturnal confusional states, an absence of a family history of dementia and the presence of risk factors for vascular disease also increase the likelihood that there will be diagnosis of vascular dementia neuropathologically confirmed. Death in these patients is usually due to the recurrence of a stroke or ischaemic heart disease. Neuropsychological testing is not especially informative in the diagnosis of vascular dementia as, typically, there is a 'mixed picture' of neuropsychological deficits. By contrast , the predominance in Alzheimer's disease of aphasia, apraxia and the visuospatial difficulties can be of considerable diagnostic value. Likewise, slowly progressive dementias without vascular risk factors and in the absence of neurological signs are rarely attributed to vascular disease at autopsy.

Binswanger's disease is a well-recognised sub-type of vascular dementia and is probably the most frequently encountered of the uncommon causes of dementia.[13] A diagnosis of Binswanger's disease is rarely made with confidence in life and such uncertainty is attributable partially to the plethora of diagnostic synonyms for it: subcortical arteriosclerotic encephalopathy, subcortical ischaemic leucoencephalopathy, subcortical ischaemic disease, etc, and to the wide spectrum of underlying pathological changes. A subcortical arteriosclerotic encephalopathy may have diverse causes, can be associated with pseudobulbar palsy and often coexists with multiple lacunar infarcts. The clinical features of Binswanger's disease are varied; men and women are equally affected; age at onset is usually less than 67 years and; almost all patients are hypertensive.

Most show a slowly progressive dementia with superimposed cerebrovascular events i.e. transient ischaemic attacks and small strokes, often with lengthy intervals between such episodes. Neurological deficits such as impaired speech, gait and balance are among the more consistent clinical features. Table 1 lists several other rare causes of dementia that comprise fewer than 3% of all cases of vascular dementia and their clinical features are well described by Lishman.[14]

Neuroradiological diagnosis

Magnetic Resonance Imaging (MRI), Computed Tomograms (CT) and Single Photon Emission Computed Tomography (SPECT) are used variously to investigate dementia sufferers. In vascular dementia, gross neuropathological findings of localised or generalised atrophy, occasionally with coexistant subdural haemorrhage, are readily detectable in life by neuroradiological studies. Likewise, ventricular dilatation and scattered infarcts can be demonstrated by CT. Pathological changes in white matter are detected more sensitively by MRI. SPECT imaging is now widely available and has become the investigation of choice in this condition; improvements in technical quality and quantification of SPECT-detected changes are now feasible but are not often undertaken in most neuroradiological centres.

For the practising clinician, the question is often which investigation would be most helpful to establish a diagnosis of vascular dementia. Unfortunately the literature on brain imaging in dementia is not yet truly informative. In the case of SPECT, reports compare most often SPECT findings with the clinical diagnosis which is inexact and sometimes with the neuropathological diagnosis and these are difficult to evaluate.[15-18] An experienced neuroradiologist can detect changes in cerebral blood flow on SPECT examination that are more typical of vascular dementia than of Alzheimer's disease, and in this respect the study of Bonte *et al*[15] is particularly informative. Their sample comprised 261 patients of whom 54 had an autopsy-confirmed diagnosis: assessments of sensitivity (86%) and specificity (73%) supported their conclusion that SPECT is useful in the early diagnosis of dementia and valuable in the discrimination between dementia subtypes.

When SPECT is combined with MRI and the results related to neuropathological findings, discrimination between the sub-types of dementia is much improved. This 'dual scan' approach can be considered as costly but when used judiciously to investigate subjects with early cognitive impairment, and for whom effective interventions are already available to slow or even reverse cognitive deficits, then the potential benefits much outweigh the expenses involved.

The issue of when to request brain imaging in routine clinical assessment of dementia sufferers has not been resolved. Clinical and laboratory procedures to investigate dementia seek first to identify potentially reversible causes if cognitive decline (e.g. silent infection, cerebrovascular insufficiency, endocrinopathy, malnutrition and metabolic disturbances) and then to separate dementia into its subtypes. These procedures are convenient and inexpensive.[19] Requests for brain imaging are expensive and frequently distressing for some dementia patients and are thus more difficult to justify. Hospital-based neurologists probably tend to make more requests for imaging than community-based geriatricians or psychiatrists; they also tend to see more patients with secondary dementias responsive to interventions. From time to time, organisations set out recommendations and guidelines for requesting such diagnostic procedures. Chui and Zhang[20] comprehensively assessed 119 consecutive referrals to a memory clinic in order to evaluate the recommendations of the American Academy of Neurology

for the investigation of dementia. The authors concluded that the results of brain imaging affected the care of 15.1% of patients when other clinical and laboratory findings were available. It is highly relevant to consider UK practice in these matters especially as treatments for primary degenerative dementias (donezepil and rivastigmine in Alzheimer's disease) and vascular dementia (see below) are now available.

RISK FACTORS

There is now good evidence to link sustained hypertension (HBP) - treated and irrespective of its control - with brain abnormalities detectable on MRI. Skoog *et al*[21] reported a 15-year longitudinal follow-up study of HBP and dementia in old people. Subjects with white matter lesions detected by CT at the age of 85 years had higher blood pressures at the age of 70 years than subjects without such lesions. The same sample revealed non-demented subjects with white matter lesions scored less well on tests of verbal and spatial ability, perceptual speed, second remembering and a cognitive screening test - the mini mental state examination.[22] The precise nature of such white matter lesions, their relationship to normal ageing processes, cognitive impairment and vascular dementia remains uncertain.[23]

Risk factors for stroke are associated with impaired cognitive function in subjects who have experienced a stroke.[24] Diabetes, hypertension and hyperlipidaemia probably exert this effect by causing atherosclerotic disease and may in turn cause multiple scattered 'silent infarcts' as cerebral blood flow is reduced, and these impair cognitive functions. In 598 healthy, elderly people in Edinburgh (the HOPE studies), systolic blood pressure could not be correlated with performance on a general test of mental ability,[25] suggesting that cognitive impairment in late life may be part of a range of conditions that includes stroke and vascular dementia all of which may share disease mechanisms. A somewhat different interpretation of the association between vascular risk factors and dementia was proposed by Prince *et al*.[26] Advantages of rural over urban residence were noted in 1,545 recruits to the MRC elderly hypertension study in terms of the relative risk of dementia; these workers argued for the existence of a previously undescribed non-familial form of dementia 'transcending traditional categories of multi-infarct dementia and AD'. Further epidemiological studies have not suggested comparable explanations preferring to link cardiovascular disease to cognitive impairment through conventional cerebrovascular disease mechanisms.[27] Elsewhere, reports of an association between low blood pressure and dementia are interpreted as a complication of Alzheimer's disease in which the central cholinergic deficit contributes to hypotensive dysregulation.[28]

Subjects with controlled HBP show increased left ventricular size and varying degrees of cortical atrophy. Mentis *et al*[29] used Positron Emission Tomography (PET) to examine the functional consequences for cerebral metabolism of these brain changes associated with HBP. They concluded that some brain areas, particularly the 'border zone' between anterior and the middle cerebral arteries territories, were particularly susceptible to the effects of HBP even though neuropsychological deficits could not be detected in the subjects. The same research group used MRI to estimate brain size in treated HBP and found that hypertensive subjects have significantly larger ventricles than normotensives.[30] Taken together, these findings suggest that there are long-term brain changes in well-controlled, treated hypertensive subjects. As yet it is unclear if brain changes are the direct consequence of HBP or are associated with a related disease process.

Longitudinal studies will reveal if the changes are progressive. DeCarli *et al*[31]

demonstrated in a different patient that white matter lesions were associated with increased systolic HBP, brain atrophy, reduced cerebral metabolism and lower scores on tests of frontal lobe function than healthy age-matched controls. Studies of this type are of considerable relevance to understanding the pathogenesis of vascular dementia and raise questions about the likely impact of current antihypertensive regimens on the prevention of vascular dementia and the nature of white matter lesions.

Much was demonstrated in earlier neuropathological studies, but modern neuroradiological examinations reveal the spectrum of brain pathology associated with HBP. It is tempting to hypothesise that a disease process (which also causes HBP) progressively damages brain structures and connections, and is unmodified by antihypertensive drugs. Initially, the effects of such damage may be lessened by inbuilt neuronal redundancy ('the cerebral reserve hypothesis') from pulsating cerebral blood vessels in which the internal pressure was raised, but eventually two pathologies: (a) progressive mechanical damage induced by hypertension and (b) a separate disease process that also causes hypertension and white matter lesions, exceed the cerebral reserve and the symptoms of vascular dementia emerge.

Treatment of vascular dementia

The treatment and prevention of dementia and/or cognitive impairment attributable to cerebrovascular disease has formerly received scant attention[31] and, for many, vascular dementia remained the last redoubt of 'essential hypertension'. The poor cognitive performance of a hypertensive patient with vascular dementia, whilst in part caused by mechanical damage, still requires the enhanced cerebral blood flow caused by increased pressure in order to maintain minimum cognitive performance. In these terms, the hypertension was 'essential' and to lower blood pressure would not improve but worsen cognitive performance. Certainly, clinical experience with first generation antihypertensive agents seemed to support this view. It was not until the paralysing effects of these drugs on the autoregulation of cerebral blood flow were recognised and more satisfactory agents became available that the benefits of reduction of blood pressure in hypertensive old people with dementia were established.[33,34]

A programme of research at the Baylor College of Medicine, Texas, provided the first truly systematic account of the epidemiology, prevention and treatment of a large cohort of patients with vascular dementia.[35] Their research consolidated risk factors for stroke and vascular dementia (Table 3), and set about seeking to slow the progress of dementia by reduction of exposures to risk factors or reversal of their effects. The best-established risk factors for vascular dementia are hypertension, heart disease and smoking.[36] The Baylor College group recommended that in vascular dementia it was worthwhile to seek to slow the disease process essentially by prevention of the recurrence of small scattered cerebral infarcts by (a) controlling hypertension, (b) reduction of platelet aggregability, (c) lowering blood lipids if raised, and (d) removal of extracerebral sources of embolic stroke (atrial fibrillation, carotid atherosclerosis).

Over the past decade, the treatment of stroke has progressed. Firstly, improved techniques of brain imaging have revealed the localisation, severity and potential reversibility of stroke-associated ischaemic lesions. Secondly, extra-cerebral sources of stroke are also now better addressed, and improvements have been made in understanding the contribution of changes in the aggregability of blood. These neuroprotective advances in the prevention and management of acute stroke should prove relevant to vascular dementia.

The purposes of neuroprotective strategies are either to prevent ischaemic injury

TABLE 3
Risk factors for cognitive impairment in late life.

Risk factor	Vascular dementia	Alzheimer's disease
clinical/demographic		
hypertension	+++	+
hypotension	0	+
male sex	++	0
female sex	0	++
smoking	+++	?(+)
socioeconomic deprivation	+++	0
poor diet	++	0
diabetes	++	0
genetic		
apolipoprotein E ε4	+	+++ (late onset)
CADASIL	+	? linked to presenilins
presenilins I and II	? linked to CADASIL	++ (early onset)
genes for hypertension	++	?
genes for diabetes	++	?

or, if injury has already occurred, to prevent further injury. Figure 1 summarises the cascade of events that follows ischaemic brain injury and which leads to neuronal death. Understanding these processes leads to the development of novel therapeutic strategies, many of which appear diverse in their proposed mechanisms of action but share the common property of slowing or preventing neuronal death.

CONCLUSION

Vascular dementia is now the focus of a much improved and more prolific research effort. Although molecular genetic advances are few in this area, there is no shortage of attractive novel hypotheses on causes, treatment and prevention. The recognition of a spectrum of neuroradiological and neuropsychological deficits, that extends from the controlled hypertensive old person who is cognitively intact to the post-stroke demented patient, is evidence of useful progress. How best to prevent cognitive decline in late life is unclear. It is certain, however, that the eventual effective strategy will address the prevention of cerebrovascular disease and is likely to involve the modification of central neuronal mechanisms implicated in the pathogenesis of some types of hypertension.

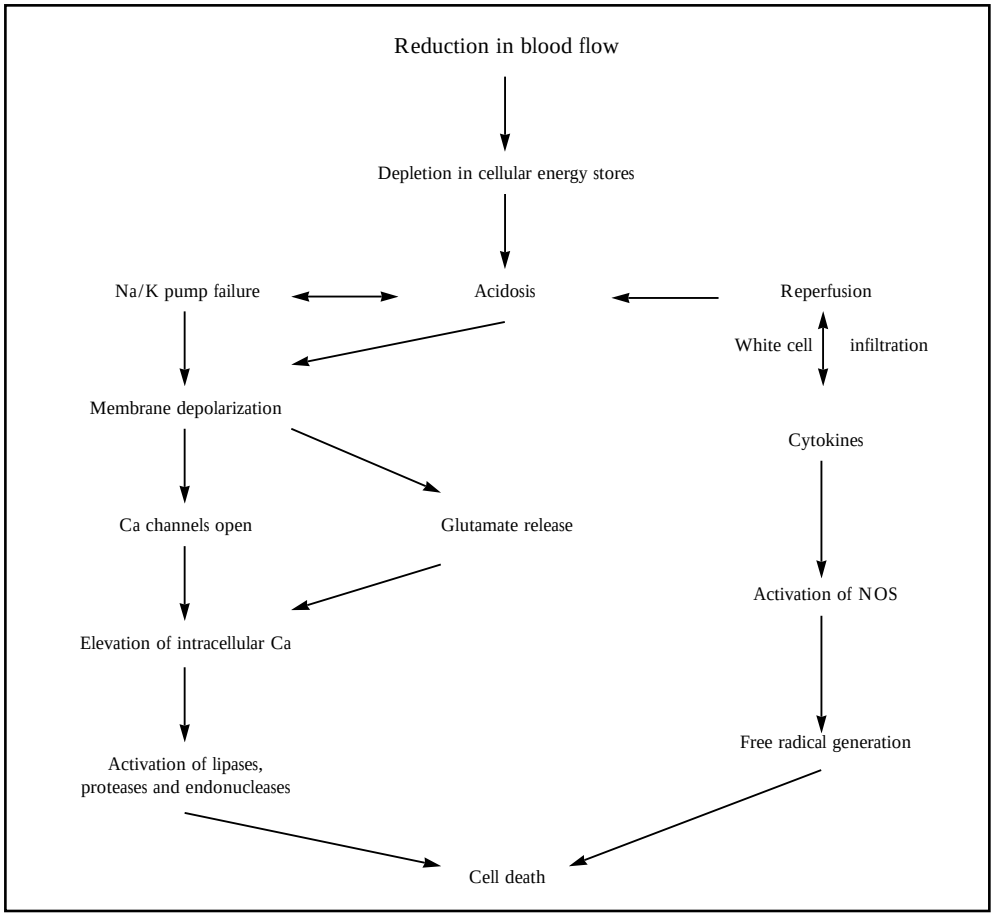

FIGURE 1

The ischaemic blood flow that leads to neuronal death in ischaemic vascular dementia. Neuroprotective therapy aims to lessen the neurotoxic consequences of ischaemic change at each step of the cascade. Agents include voltage-sensitive calcium channel antagonists (e.g. nimodipine), noncompetitive N-methyl D aspartate receptor antagonists (e.g. dextromorphan) calcium channel modulators (e.g. eliprodil) and antioxidants.

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