Fortnightly Review

Vascular dementia

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At the turn of the century cerebral atherosclerosis, by causing chronic strangulation of the blood supply to the brain, was thought to be the commonest cause of dementia. Alzheimer's disease was regarded as a rare cause of dementia affecting only younger patients (presenile dementia). By the 1950s, however, Alzheimer's disease was known to be much more common than originally realised, affecting older as well as younger patients, and it had been discovered that atherosclerosis of the cerebral blood vessels could be present in normal elderly subjects as well as in those who were cognitively impaired.[1]

In 1970 Tomlinson *et al* classified the pathological changes after death in patients with dementia into two main groups: *(a)* changes typical of Alzheimer's disease (neurofibrillary tangles and plaques on microscopy) and *(b)* areas of brain softening or infarction (a smaller group).[2] Tomlinson *et al* labelled the latter group as indicating atherosclerotic dementia. In 1974 Hachinski and colleagues used the term multi-infarct dementia to describe the mechanism by which they considered vascular dementia was produced.[3] However, although multiple cerebral infarcts can cause dementia, other pathogenetic mechanisms may be as important, or more important. The terms multi-infarct dementia and vascular dementia should not therefore be used synonymously.

In this review we concentrate on ischaemic vascular dementia rather than that caused by haemorrhage (such as subdural haematoma, subarachnoid haemorrhage, and haemorrhages caused by cerebral amyloid angiopathy) or hypoxia.

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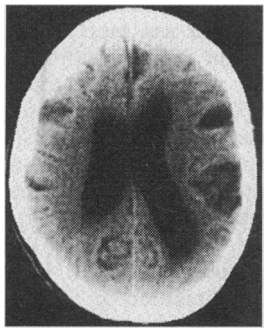

Fig 1—*Computed tomography of the brain of patient with multi-infarct dementia showing multiple cortical infarcts*

How common is vascular dementia?

Vascular dementia is probably the second commonest cause of dementia (after Alzheimer's disease), although some authorities believe that senile dementia of the Lewy body type may be more common than vascular dementia.[4-6] In one epidemiological study vascular dementia was even more common than Alzheimer's disease in those aged over 85 years—that is, a reversal of the trend in younger subjects.[7]

Table 1—*Vascular dementia in studies done at postmortem examination. Values are numbers (percentages) of cases*

	No of cases	Alzheimer's disease alone	Vascular dementia alone	Alzheimer's disease and vascular dementia combined
Tomlinson *et al* (1970)[2]	50	50	18	18
Todorov *et al* (1975)[8]	675	31	18	36
Wade *et al* (1987)[9]	65	58	9	15
Jellinger *et al* (1990)[10]	675	60	16	10
Gilleard *et al* (1992)[11]	64	38	33	16

Summary points

- Symptomatic stroke increases the risk of dementia more than ninefold
- Vascular dementia is one of the three commonest causes of dementia
- Above the age of 85 years it may be commoner than Alzheimer's disease
- Vascular dementia may be caused by multiple infarcts, white matter ischaemia, or a strategically placed infarct
- All patients with possible vascular dementia need careful assessment to detect any underlying causes and risk factors that might be remediable

Different histopathological studies have reported that multi-infarct dementia is the sole cause of dementia in 9-33% of patients with dementia and contributes to dementia in a further 10-36% of cases (table 1).[8-11]

It is difficult, however, to estimate the exact prevalence of vascular dementia as different diagnostic and pathological criteria have been used in different studies, and some investigators believe that vascular dementia is overdiagnosed while others believe that it is underdiagnosed.[12,13] Ischaemic white matter lesions —which may well contribute to dementia—are increasingly being recognised as being visible on computed tomograms and magnetic resonance images of the brain, implying that vascular dementia may have been grossly underdiagnosed. On the other hand vascular dementia may have been overdiagnosed for several reasons—for example, a diagnosis of vascular dementia simply because of a history or neuroimaging evidence of a stroke (even in the absence of a temporal relation between the stroke and dementia).

Mechanisms of vascular dementia

MULTI-INFARCT DEMENTIA

Figure 1 shows a computed tomogram of the brain of a patient with multi-infarct dementia. Infarcts can be in the cerebral cortex, subcortical areas, or more commonly in both cortical and subcortical sites. Dementia will undoubtedly follow if sufficient brain tissue is damaged. Tomlinson *et al* estimated that at least 100 ml of brain tissue would need to be lost before dementia was produced.[2] Further studies showed, however, that the site of the cerebral infarction is more important than the volume of tissue lost.[14,15] Dementia is thought to be produced by this loss of brain tissue, but the effect of multiple infarcts could even be synergistic rather than cumulative,[16] although our knowledge of the exact mechanisms of vascular de-

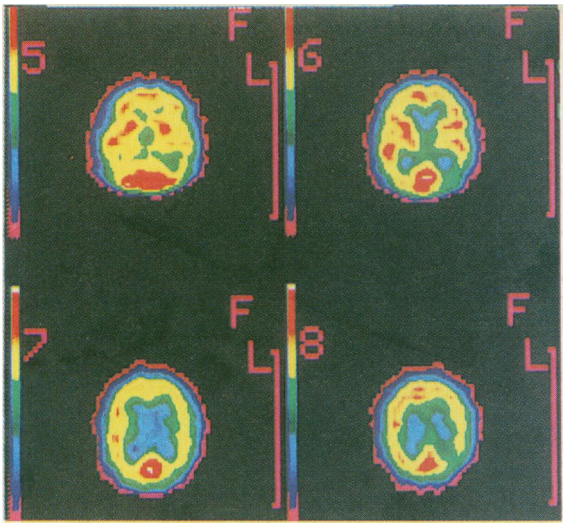

Fig 2—*Single photon emission tomogram of patient with angular gyrus syndrome showing reduced cerebral blood flow (green) to left temporoparietal region*

mentia is far from complete. Multiple cortical infarcts are commonly the result of thromboembolic disease—for example, from a cardiac or carotid source—but can also be caused by cerebral vasculitis.

Multiple lacunar infarcts can also cause dementia, and Marie, in 1901, was the first to describe the symptomatology of lacunar dementia: hemiparesis, small stepping gait (marche à petits pas), dysarthria, dysphagia, and cognitive impairment.[17] Patients with the ensuing subcortical dementia usually show signs of psychomotor slowing, poor concentration, indecision, and mental apathy, unlike patients with predominantly cortical infarcts, who often display signs of cortical dysfunction such as amnesia, aphasia, apraxia, and agnosia. Lacunar infarcts are often associated with white matter ischaemia, and both conditions are usually seen in patients with hypertension.[18,19] Rarely,

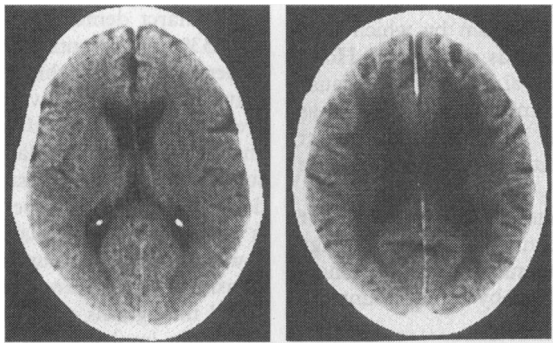

Fig 3—*Left: Computed tomogram of the brain showing normal appearance of white matter. Right: Computed tomogram of the brain showing extensive low attenuation of white matter (leukoaraiosis)*

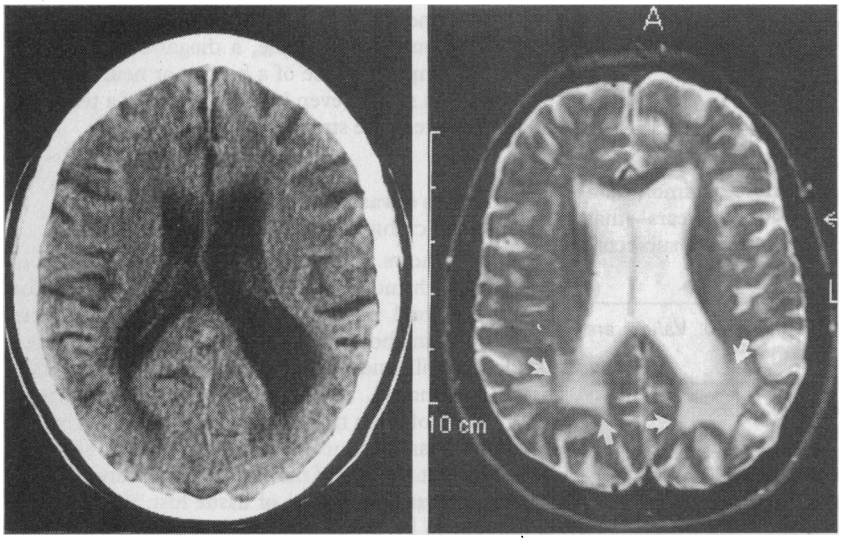

Fig 4—*Left: Computed tomogram of brain showing moderate degree of low attenuation of white matter. Right: Magnetic resonance image of brain of same patient showing more extensive white matter hyperintensities (arrows)*

they are seen as part of the syndrome of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[20] In this hereditary disease, in which genetic analysis shows a linkage to chromosome 19, patients have recurrent stroke-like events with visible white matter lesions on neuroimaging and subcortical dementia.

SINGLE STRATEGICALLY PLACED INFARCTS

Little doubt now exists that vascular dementia can be produced after even a single infarct if this is located in a strategically important area of the brain. The angular gyrus syndrome, for example, is a dementia that may follow infarction of the angular gyrus, which is situated in the inferior parietal lobule (fig 2). Patients with the angular gyrus syndrome used to be commonly misdiagnosed as Alzheimer's disease. They present with acute onset of fluent dysphasia, visuospatial disorientation, agraphia, and memory loss.[21] Thalamic dementia can follow thalamic infarction, especially paramedian thalamic infarction, and can present with a syndrome of drowsiness, ocular palsies, apathy, and slowness, together with memory loss.[22] Other recognised strategic areas include the caudate and globus pallidus, basal forebrain, and hippocampus.

WHITE MATTER ISCHAEMIA

This may be the commonest mechanism producing vascular dementia. Binswanger's disease, described by Otto Binswanger in 1894 before Alzheimer provided the histopathological description in 1902, was regarded as a rare form of dementia caused by ischaemia to the white matter. Although Binswanger's disease was originally a pathological rather than clinical description, it is thought to result in a slowly progressive intellectual impairment, with recurrent stroke-like events.[23] A consistent pattern of clinicopathological correlation has not been easy to establish, however, and some features can often be clinically misleading, such that the differential diagnosis—for example, from Lewy body dementia and Parkinson's disease with dementia—can be difficult. Helpful diagnostic criteria are nevertheless emerging.[6,24,25]

After computed tomography was introduced in clinical practice it was realised that rarefaction or low attenuation of the white matter was much more common than previously thought (fig 3). Although low attenuation of the white matter, also termed leukoaraiosis by Hachinski (Greek: leuko=white, araiosis=rarefaction), can occur for various reasons—for example, after head injury or cerebral irradiation—age and ischaemia to the white matter are regarded as the commonest causes.[26–28] Pathologically, low attenuation of the white matter represents areas of demyelination and reactive gliosis together with arteriosclerotic changes with hyalinisation or fibrosis and thickening of the vessel walls, accompanied by narrowing of the lumina of the small penetrating arteries and arterioles in the white matter.[29]

Magnetic resonance imaging is more sensitive than computed tomography, showing more white matter lesions (fig 4). Most investigators, however, believe that some of these changes, such as pencil thin haloes around the ventricles, are age related physiological changes of little clinical importance, although more florid changes, such as hyperintense patches, are certainly pathological.[30–32] The vulnerability of the white matter to ischaemia is due to the fact that it is supplied by long penetrating end arterioles from the surface and base of the brain that travel for a long distance with very little anastomosis (fig 5).

Computed tomography of the brain shows that about 10% of normal elderly subjects have evidence of low attenuation of the white matter, but the incidence increases with age, and by the age of 85 years it

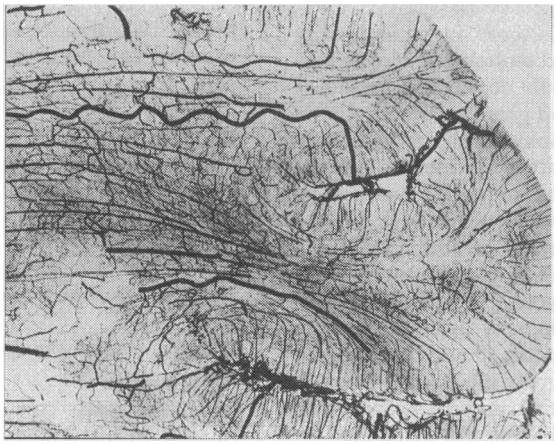

Fig 5—*Whole brain injection of a micro-opaque aqueous solution showing short straight arterioles supplying the cerebral cortex and subcortical arcuate fibres, preserved in Binswanger's disease, and long penetrating arterioles supplying white matter*

is 30%.[27] Magnetic resonance imaging shows the incidence approaching 100% at age 85. Recent studies have shown that normal subjects with low attenuation of the white matter could have subtle neuropsychological deficits such as a slower rate of mental processing and impaired attention and concentration.[33–36] These deficits are compatible with the subcortical location of these lesions. White matter lesions are seen in 70-90% of cases of vascular dementia, while in Alzheimer's disease the incidence varies from 10-20% in early onset disease to 70-80% in patients with late onset.[27 37 38] White matter lesions are associated with hypertension and, in some studies, with heart disease and diabetes.[39–41] They are thought to cause dementia by disconnecting the pathways between the cortical and subcortical centres.

Factors associated with increased risk of vascular dementia

- Age
- History of stroke
- Low education
- Hypertension
- White matter lesions
- History of myocardial infarction
- Diabetes
- Cerebral atrophy
- Cortical infarcts
- Left hemispheric stroke
- Early urinary incontinence
- Falls

Dementia after stroke

It is not known if the risk factors for developing vascular dementia differ from those found in stroke. Stroke and age, however, are the most important risk factors for developing dementia, and stroke by itself increases the risk of dementia ninefold.[42] Although dementia after stroke is likely to be related to cerebrovascular disease, it could also be caused by a subclinical degenerative condition, such as Alzheimer's disease, that has simply been brought to light earlier by the stroke, as conditions such as Alzheimer's disease and stroke are both common in the elderly.

Tatemichi *et al* assessed 251 patients three months after the onset of stroke and discovered that just over a quarter were demented.[42] Factors associated with increased risk of dementia included advancing age, low education, history of stroke, diabetes, and left sided lesions.[42 43] Importantly, but not surprisingly, patients with stroke and cognitive impairment were significantly less likely to live independently, and this was regardless of their physical impairment or age.[44] Other studies have focused on comparing patients with multi-infarct dementia with similar groups of patients with multiple cerebral infarcts but no evidence of dementia.[45 46] The box at left shows some of the risk factors associated with vascular dementia.

Hachinski ischaemia scale

Item	Score value	Item	Score value
Abrupt onset*	2	Emotional incontinence*	1
Stepwise course*	1	History of hypertension*	1
Fluctuating course	2	Evidence of associated atherosclerosis	1
Preservation of personality	1	History of stroke*	2
Nocturnal confusion	1	Focal neurological symptoms*	2
Depression	1	Focal neurological signs*	2
Somatic complaints*	1		

*Discriminating items of the Hachinski score after validation at postmortem examination[49]

Diagnosing vascular dementia

The diagnosis of vascular dementia can be straightforward in patients with a clear history of strokes and cognitive impairment when a temporal connection exists between stroke and cognitive decline. More often, however, it is difficult to determine whether cerebrovascular disease alone causes dementia, whether it merely contributes to the dementia, or whether it is simply a coincidental finding. Various diagnostic criteria exist to aid diagnosis.

On the Hachinski ischaemic scale vascular dementia is diagnosed when the patient is given a score of 7 or higher.[47] Although the Hachinski scale is widely used, particularly for research purposes, it has poor inter-rater reliability, and modified versions have been proposed (box).[48 49]

The American Psychiatric Association publishes criteria for diagnosing psychiatric illnesses including dementia in the *Diagnostic and Statistical Manual of Mental Disorders*, which is regularly updated, most recently in 1993 (DSM-IV).[50] The criteria have not been validated and are regarded as being subjective.

The World Health Organisation produces criteria for the international classification of diseases (ICD-10, the 10th revision, is the latest).[51] Vascular dementia is subclassified into vascular dementia of acute onset, multi-infarct dementia, subcortical vascular dementia, and mixed or unspecified types.

More recently two new sets of criteria have been proposed, one by the State of California Alzheimer's Disease Diagnostic and Treatment Centre (ADDTC)[25] and the other by the National Institute of Neurological Disorders and Stroke and a European panel of experts (NINDS-AIREN).[52] Both require the presence of *(a)* dementia, *(b)* cerebrovascular disease, and *(c)* a relation between the two (such as onset of dementia within three months of a stroke).

Recent reports suggest that the criteria proposed by the Alzheimer's Disease Diagnostic and Treatment Centre could be more sensitive than the Hachinski scale, although validation studies of postmortem examinations are awaited.[53 54]

All the above criteria are based on the multi-infarct concept of vascular dementia except for those of the ICD-10 and of the National Institute of Neurological Disorders and Stroke and expert panel.

Assessment of patients and differential diagnosis

In a patient with possible cognitive impairment an accurate and detailed history from the patient and carer, as well as a full physical examination, is essential. Special attention needs to be given to *(a)* detection of vascular risk factors, including hypertension, heart disease, and diabetes; *(b)* examination of the cardiovascular system, which is often a cause for thromboembolism (atrial fibrillation, heart failure, valvar heart disease, carotid stenosis); and *(c)* neurological examination, which may show evidence of focal neurological deficits such as pyramidal tract signs, dysarthria, hemianopia, or extrapyramidal signs. Psychometric assessment is mandatory.

Investigation should include a search for treatable causes of dementia, such as hypothyroidism, neurosyphilis, vitamin B12 deficiency, normal pressure hydrocephalus, frontal lobe tumours, and cerebral vasculitis. Although uncommon, hyperviscosity syndromes and severe bilateral carotid stenosis can also lead to cerebral hypoperfusion and are treatable. Computed tomography or magnetic resonance imaging of the brain is necessary to exclude some of these treatable causes and to detect and define the extent of any cerebrovascular disease.

Other investigations may also be needed in

individual patients, such as echocardiography, ultrasonography of the carotid arteries in patients with possible carotid stenosis, and ambulatory blood pressure monitoring if there is doubt about the reliability of casual measurements of blood pressure. Single photon emission computed tomography can be more helpful than anatomical imaging in atypical patients—patients with vascular dementia tend to have asymmetrical patchy areas of reduced cerebral blood flow. Coagulation studies with measurement of antiphospholipid antibodies, protein C, protein S, and antithrombin III are often warranted in the younger patient. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy should be suspected in patients with a family history of the disease. The box at right lists investigations that may be useful when assessing a patient with possible vascular dementia.

Vascular dementia needs to be differentiated from other causes of dementia such as Alzheimer's disease, Lewy body type dementia, progressive supranuclear palsy, corticobasal degeneration, Parkinson's disease dementia, and frontal lobe tumours (box). The most difficult differential diagnosis, however, is vascular dementia accompanying Alzheimer's disease or other degenerative dementias. This diagnosis is often made only at the postmortem examination.

Useful investigations in patients with possible vascular dementia

Routine laboratory investigations
Full blood count
Plasma viscosity
Serum urea and electrolytes
Liver functions and protein electrophoresis
Thyroid function tests
Syphilis serology
Vitamin B12

Computed tomography or magnetic resonance imaging of the brain

Doppler ultrasonography of the carotid arteries

Echocardiography

Coagulation studies
Antiphospholipid antibodies, proteins C and S, and antithrombin III

Electrocardiography (including 24 hour monitoring)

24 Hour blood pressure monitoring

Single photon emission computed tomography

Treatment of vascular dementia

A search for vascular risk factors is important as vascular dementia, unlike Alzheimer's disease, is preventable, and evidence exists that controlling vascular risk factors such as hypertension and diabetes and using an antiplatelet drug can improve cognitive functioning.[59,60] Evidence exists that even in the absence of dementia vascular risk factors such as hypertension, diabetes, and hypercholesterolaemia can by themselves cause cognitive impairment.[61–63] This led some investigators to advocate identifying and treating these risk factors regardless of the cause of dementia, especially with reports of an association between vascular risk factors (such as smoking, systolic hypertension, and evidence of myocardial ischaemia in the electrocardiogram) and Alzheimer's disease.[64]

Anticoagulation with warfarin in patients in atrial fibrillation is unfortunately suitable for only a small proportion of patients because of the risk of falls and of difficulty with compliance with treatment in patients with established dementia. An antiplatelet regimen such as low dose aspirin is usually a more acceptable compromise in these patients. Those with substantial carotid stenosis should also be considered for surgery, and case reports have shown individual patients with severe bilateral carotid disease benefiting from extracranial-intracranial anastomosis. Patients with evidence of active vasculitis, either primary cerebral vasculitis or as part of a systemic vasculitis with secondary brain involvement, often benefit from immunosuppressive drugs such as corticosteroids. It is also worth identifying patients with hereditary vascular dementia as early diagnosis can allow for more aggressive treatment of any risk factors and other family members can be offered genetic counselling. Rarely, other treatable causes of vascular dementia can be detected—such as cerebral hypoperfusion secondary to a hyperviscosity syndrome or a dural arteriovenous fistula, which may need surgery or embolisation. Malignant lymphoma of blood vessels (neoplastic angioendotheliomatosis), is a rare form of B cell lymphoma that can occur in immunosuppressed patients—for example, after organ transplantation—and which may respond to chemotherapy.

In addition to treatments to modify patients' risk factors, other specific treatments are being explored. Although early studies with nootropic compounds such as oxiracetam claimed to show some benefit in multi-infarct dementia (and also in primary degenerative dementia), this approach has not generally been accepted as clinically useful. Similarly, early hopes that calcium channel blockers such as nimodipine would be of value have not been sustained. Several further strategies—for example, to protect neurones from excitotoxins or to reinforce other neuroprotective mechanisms—are under evaluation, but it is too early to be certain of their potential in the clinical context.

Differential diagnosis of vascular dementia

Vascular dementia
Typically presents with sudden onset and stepwise course of cognitive decline with history of strokes, transient ischaemic attacks, or both
Evidence of focal neurological deficit on examination (such as hemiparesis, sensory loss, extensor plantar response)
A source of thromboembolism—such as carotid disease, atrial fibrillation, or valvar heart disease—may be present
Evidence of cerebrovascular disease on computed tomography or magnetic resonance imaging

Vascular dementia and Alzheimer's disease (mixed)
Can be difficult to diagnose during life because *(a)* vascular dementia can follow a slow progressive course in almost half of patients and *(b)* it is sometimes difficult to determine the exact role of vascular lesions (such as white matter lesions) seen on neuroimaging

Lewy body type dementia[6,55]
Can also be confused with Alzheimer's disease but suspected in patients with:
- Marked fluctuations of symptoms
- Prominent extrapyramidal signs, especially rigidity and hypokinesia
- Early and florid visual hallucinations and delusions
- Poor tolerance of neuroleptic drugs

Parkinson's disease dementia[56]
Possibly affects 10-20% of patients with Parkinson's disease
Parkinsonian features usually precede the dementia
Dementia is subcortical (apathy, poor concentration, indecision)
Parkinsonian features usually respond to dopaminergic drugs

Progressive supranuclear palsy[57]
Similar to Parkinson's disease dementia but parkinsonian features are non-responsive to dopaminergic drugs
Paralysis of upward or downward gaze, or both
Truncal ataxia

Multisystem atrophy[58]
Slowly progressive dementia with any combination of:
- Pyramidal tract signs
- Extrapyramidal features
- Autonomic failure
- Cerebellar ataxia

Frontal lobe tumours
Patients can present with disinhibited and irrational behaviour or mental apathy and indecision
Symptoms and signs of increased intracranial pressure may arise late

The future

The most exciting area of research is into the exact role of white matter disease in causing or contributing to dementia as this is very common in vascular dementia and can also be seen in other dementias as well as in some normal elderly subjects. It remains to be seen if normal subjects with these changes are at increased risk of developing dementia. If they are, it suggests the need for more aggressive treatment of risk factors and closer follow up of these subjects before they become too cognitively impaired. We also need to develop a better understanding of the relation between structural pathological changes and the symptoms and signs in subtypes of vascular dementia, taking further the work of earlier studies.[65]

Another important area that will have implications for vascular dementia is the likely use of thrombolytic drugs in the treatment of acute stroke. Theoretically these will limit brain damage sustained during the stroke, but they may also increase the total number of patients surviving who would otherwise have died without this treatment, perhaps leaving more patients with considerable cognitive impairment.

Finally, as a common cause of dementia that results in immense suffering to those affected and their carers and in a huge financial burden to the health service, vascular dementia is at last coming out of the shadow of Alzheimer's disease and is generating an interest that is long overdue.

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