

**A**lzheimer first describe vascular dementia (VaD) 111 years ago. Despite this, its history has been dogged by misconceptions and it is only in the past decade that our understanding has matured.

## HISTORICAL OVERVIEW

For the greater part of the 20th century dementia was routinely attributed to arteriosclerosis and consequent chronic cerebral ischaemia. This view changed with the increasing recognition of Alzheimer's disease (AD) and the demonstration that infarcts and not chronic ischaemia were the basis of what came to be termed multi-infarct dementia (MID). The term "vascular dementia" subsequently replaced MID as it was recognised that there were many different aetiologies apart from multiple infarcts. However, by the end of the 20th century, the increasingly recognised AD overshadowed VaD to the extent that some authors reported that MID was rare. Because AD was thought to be the major cause of dementia, its criteria became those applied to all dementia. AD was separated from VaD using clinical features thought to reflect vascular risk factors, vascular events, and the manifestations of systemic and cerebral vascular disease, typically codified using the ischaemic score (table 1). The basis of the definition has resulted in the criteria for VaD emphasising memory loss and usually the progression and irreversibility of cognitive decline, none of which are necessarily the case. In addition, they also define dementia as the level of cognitive impairment at which normal daily functions are impaired and therefore will identify only late cases, so underestimating the prevalence of cognitive impairment caused by vascular disease and denying patients the benefit of early preventative treatment. Regulatory bodies, which increasingly determine what may be done and to whom, have a tendency to adhere rigidly to published data. If data exist only for advanced disease, then expensive drugs may only be available for advanced disease, at least within guidelines. This important early stage is termed vascular cognitive impairment (VCI). The importance of VCI lies in the fact that vascular disease is the largest single identifiable risk factor for dementia apart from age and the only one currently treatable. Indeed, the concept can be taken further; while the prevention of progression of VCI is analogous to secondary prevention, primary prevention requires the recognition of the presence of risk factors in a susceptible host, termed "brain-at-risk" (fig 1).

In the past five years, those working in this field have come to recognise that VCI is a far more appropriate concept than VaD, although as yet no criteria have been developed for VCI. As a result of this very recent recognition and lack of criteria there are currently few data concerning VCI; much of the established knowledge is derived from the old concept of VaD. In this paper, VaD refers to data based on the old concept and criteria, and these criteria will be critically appraised in order that the limitations of data based upon them can be appreciated.

Awareness of VCI has not been the only new development. Our understanding of VCI has advanced from MID to encompass a range of aetiologies and to the more recent realisation that it is subcortical VCI that is the most common and the most readily characterised. Subcortical VCI accounts for over 40% of all VCI and is the natural successor to Binswanger's disease in much the same way that VCI is the successor to VaD. There has been another major change in the past decade with the increasing recognition of mixed dementia—that is, where VaD coexists with other causes of dementia, particularly AD—and this is now known to be common.

## SUBCORTICAL VASCULAR COGNITIVE IMPAIRMENT

Subcortical VCI has its own history which dates back to the notion of Binswanger's disease, an outdated concept which has been reviewed by Olszewski. Binswanger's disease was rarely reported before the arrival of computed tomography (CT) scanning and magnetic resonance imaging (MRI). By 1987 only 46 cases had been reported. Throughout the last two decades of the 20th century, there were numerous reports of "Binswanger's disease" diagnosed solely by the appearance of extensive white matter changes on neuroimaging without clinical correlates. This is now recognised to be inappropriate, white matter changes without readily apparent clinical

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**Table 1** The ischaemic scale

Feature	Value
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/presence of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2
	Total score

Scores over 7 suggest a vascular aetiology for dementia, whereas scores of 4 or less do not support a vascular aetiology.

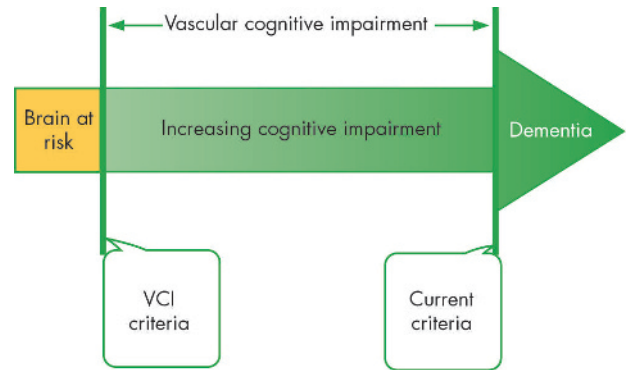
correlates being very common in the elderly, and the term “leukoaraiosis” and not Binswanger’s should be used in describing such appearances.

### TRADITIONAL DIAGNOSTIC CRITERIA

Two similar sets of criteria for the identification of VaD exist, but neither has met universal acceptance or been validated. Furthermore, they produce wildly different results and are difficult to apply consistently with poor intra- and inter-rater reliability.

The National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et L’Enseignement en Neurosciences (NINDS-AIREN) criteria define probable VaD as cognitive decline from a previously higher level of functioning in memory and two or more cognitive domains, the decline being severe enough to interfere with activities of daily living. Evidence of cerebrovascular disease on both clinical examination and neuroimaging is required, as is evidence of a relationship between the stroke and cognitive decline, which can be provided by two of the following: (1) onset of dementia within three months after a recognised stroke; (2) abrupt deterioration in cognition; and (3) stepwise deterioration. Abnormalities on neuroimaging are only considered to support the diagnosis of VaD if they fulfil criteria regarding site and size—for example, large vessel strokes in the following sites: bilateral anterior cerebral, posterior cerebral, association areas or carotid watershed (superior frontal, parietal); small vessel disease in the basal ganglia and frontal white matter; extensive periventricular white matter lesions; or bilateral thalamic lesions. The criteria for severity specify that leucoencephalopathy must involve at least 25% of the total white matter. The radiological criteria can be difficult to apply in practice without a combination of experience, operational guidelines, and training.

A diagnosis of possible VaD is made: (1) if there are no neuroimaging data but there is clinical evidence of cerebrovascular disease; or (2) in the absence of a clear temporal relationship between dementia and stroke; or (3) in those with a subtle onset and variable course. Haemorrhagic lesions are permitted. Definite VaD is diagnosed provided probable dementia exists, it is accompanied by histopathological evidence of cerebrovascular disease, and there is no histopathological evidence of other possible causes of the cognitive loss. VaD is excluded in cases with disturbed consciousness, psychosis, severe aphasia, major sensorimotor deficits, or



**Figure 1** The evaluation of vascular cognitive impairment.

other brain diseases such as AD that could themselves account for the deficit. Mixed dementia is not recognised, but the coexistence of AD is termed AD with cerebrovascular disease.

The California criteria are not fundamentally different, but differ in details. Haemorrhagic and anoxic lesions are not included. The number and type of cognitive defects are deliberately not specified, but the loss should be sufficient to interfere with the conduct of the patient’s customary affairs of life and should not be confined to a single narrow category. Two or more ischaemic strokes (at least one of which is outside the cerebellum) or one stroke with a clear temporal relationship to the onset of dementia are required. Risk factors and some clinical features are included as supportive features, but how these are to be operationalised is not stated.

It is important to note that these criteria were developed by committee and are supported by little evidence. They cannot be used to define the manifestations of VaD and are at risk of tautology. For example, analysis of case series meeting current criteria for VaD should reveal memory loss in all cases. This may be taken as showing that memory loss is universal in VaD. This is so only because it is defined that way. If the criteria are wrong, so is case identification.

Despite inappropriate selection for memory loss, the data so far identify a variety of patterns of cognitive loss beyond this, the differing patterns often depending on case selection. The predominating theme is, however, of a primary subcortical dementia with early impairment of frontal lobe function. Memory is involved but is often not pre-eminent. The presence of “patchy” or unequal cognitive deficits is a requirement for a diagnosis of VaD in the International classification of diseases, 10th revision (ICD-10), but this pattern of cognitive loss is only to be expected in true MID where there are only very few (two or three) cortical infarcts. Not only this, but where “patchiness” can be measured, it is not different in quantity between VaD and AD, it is just that the affected domains are different.

### EPIDEMIOLOGY

The incidence of VaD, using the old criteria, is about 3.8 per thousand per annum. The incidence in women rises from between 0.3 and 1.36 in those aged 65 to 69 years, to 9.3 in those aged 85 or over. For men the corresponding figures are between 1.3 and 2.2 to 9.3 and 15.9 in those aged over 90. Dementia from all causes has a prevalence of about 8% over the age of 65. Between 9–39% (but typically 13–19%) of these

cases are vascular, but VaD may account for half of Japanese cases. An additional 11–43% may be mixed dementia. The proportion of cases due to VaD falls with increasing age but even so, the prevalence of all dementia rises so rapidly with age that the prevalence of VaD also rises, from 0% to 2% in the 60–69 year age group to up to 16% for males aged 80–89, though more typical figures are between 3–6%. Males are more commonly affected than females.

The limited number of cases reported makes estimating the incidence and prevalence of subcortical VaD impossible. Some limited data are, however, available. In a sample taken from a veterans' hospital, 43% of 125 patients referred to a prospective study of multi-infarct dementia had lacunes alone as the explanation.

Data are now becoming available concerning the epidemiology of VCI. In patients under 74, VCI may be the single most common cause of cognitive impairment. In those aged 75–84, cases of pure VCI, VaD, and those with a vascular component in the context of mixed disease outnumber those with pure AD. Patients with VCI are more likely to die or become institutionalised than those with early AD who are not yet demented. VCI is associated with both stroke and death from stroke.

### AETIOLOGY AND PATHOPHYSIOLOGY

“Vascular dementia” is often used as if it refers to only one condition and research is often done on the same basis. However, there are many aetiologies leading to differing patterns of cerebral lesions in turn producing varying clinical manifestations and psychological deficits. An integral part of a diagnosis of VCI should be a statement concerning the aetiology because the treatment is that of the underlying cause.

### LEUKOARAIOSIS

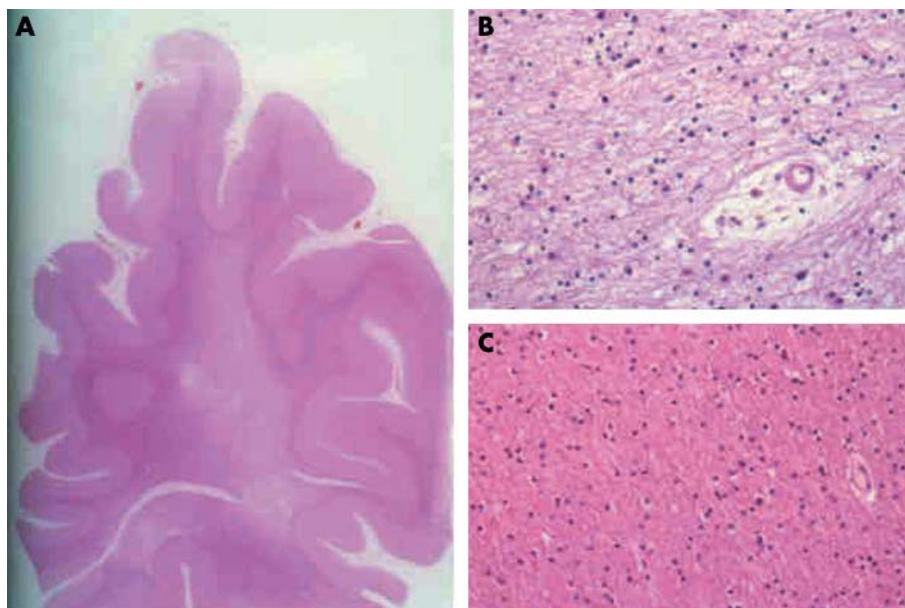
In VCI the earliest changes are usually those of small vessel disease producing white matter changes. These are conveniently termed “leukoaraiosis” or thinning of the white matter (fig 2). The term “leukoaraiosis” encompasses a range of pathologies and was originally used in the context of CT white matter changes but it is also used to refer to white matter

changes on MRI. However, a wide range of structural changes encompassing increased water content without functional loss through to axon or myelin loss appear similar or identical on MRI. This is one of the reasons for the relatively poor correlation between leukoaraiosis and cognition.

Deep white matter changes seen on MR correspond to myelin pallor on naked eye examination of slides when the MR changes are over 10 mm. The subcortical U-fibres are spared. Axons, myelinated fibres, and oligodendrocytes are decreased in the affected areas, and spongiosis is seen in the same areas. These changes blend gradually into surrounding tissue. Frank infarction is rare in lesions corresponding to leukoaraiosis, but is otherwise a common part of the pathology of the deep white matter. Small punctate lesions seen on MR correspond to dilated perivascular (Virchow-Robin) spaces. When seen in the periventricular regions, leukoaraiosis is often caused by breakdown of the ependyma, with increased fluid content of the local white matter with some loss of myelin and dilated perivascular spaces, and is therefore less closely linked to hypertension. The blood–brain barrier breaks down in regions of leukoaraiosis and plasma proteins can be found in glial cells in close relation to leukoaraiosis. Whether these changes are causal or merely consequences of ischaemia remains to be established, although extravasated plasma proteins are known to be neurotoxic.

Leukoaraiosis is aetiologically associated with hypertension but not with carotid disease. Episodic hypotension occurring through transient dysrhythmias, nocturnal hypotension, or carotid sinus hypersensitivity superimposed on a background of diminished vascular reserve may be one group of aetiological mechanisms for both leukoaraiosis and incomplete infarction which comprises zones of partial neuronal or axonal loss with demyelination, increased perivascular spaces, reactive astrocytosis, gliosis, and sparse macrophages. It is thought to occur as a result of repeated episodes of hypoperfusion, sufficient to damage tissue but not sufficient to lead to frank necrosis.

There is increasing evidence for genetic susceptibility. This might be suspected as the accepted risk factors explain only



**Figure 2** Leukoaraiosis. (A) Coronal section through a frontal lobe in a patient with prominent leukoaraiosis on magnetic resonance imaging (MRI). There is extensive but irregular pallor of white matter in the absence of lacunes (haematoxylin and eosin (H&E)). (B) High power view of the pale white matter area, showing rarefaction of the tissue, persistence of oligodendrocytes, and the presence of reactive astrocytes. (C) High power view of the dark white matter areas, showing the normal histology (H&E). Figures courtesy of Dr DG Munoz.



part of the development of leukoariosis. It is a common clinical experience that leukoariosis is not directly related in severity to hypertension in all patients and there is now direct evidence that genetic factors play an important part in the susceptibility of vessels to damage and in the development of leukoariosis. There are now also two clearly inherited conditions: cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), where the pathological basis is periodic acid-Schiff positive material distributed around smooth muscle cells in the walls of affected cerebral vessels; and another autosomal recessive disease of small vessels including lumbago and alopecia most often reported from Japan. It also seems probable that there are other, as yet unidentified, conditions that are relevant here.

There is also evidence for impairment of axonal transport, perhaps also on an ischaemic basis, and diffusion tensor imaging shows changes outside regions that are abnormal on standard MRI.

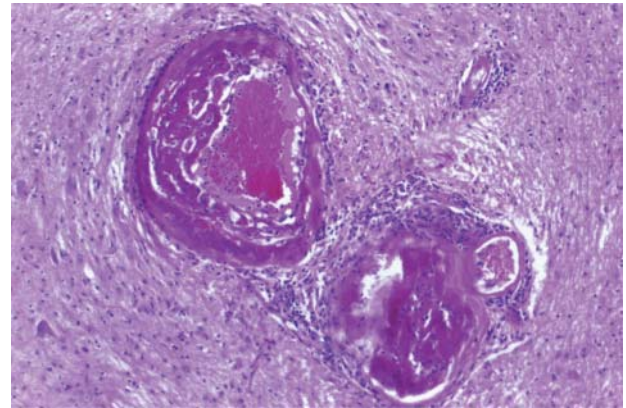
Early reports on the effects of leukoariosis on cognition were mixed. In part this was because some studies used insensitive measures of cognition and others used insensitive rating scales to quantify leukoariosis. This uncertainty was supported by the fact that more than 90% of elderly individuals have some form of leukoariosis without necessarily exhibiting obvious cognitive deficits. However, there is now clear evidence that leukoariosis is associated with both cognitive impairment, particularly the attention and speed components of executive function, and focal signs in otherwise normal individuals; even in early VCI there is a weak association between leukoariosis and cognitive loss. Functional imaging (diffusion tensor MRI) shows abnormalities of diffusivity in normal appearing white matter in patients with leukoariosis and diffusivity correlates better with cognition than simple lesion load.

### INFARCTS

Infarcts contribute to most cases of VCI, but multiple smaller infarcts and small vessel disease are more often a substrate of VCI than single major infarcts. Early work on VaD often concentrated on infarct volume with debate over the minimum volume of infarction needed to produce dementia and implicated volumes over 20 ml, and in particular over 50 ml. In more modern work, smaller volumes, usually in the range of 1–30 ml, are more typical and low volumes (mean of 8 ml) correlate with cognitive status in VCI. More recently much less attention has been paid to infarct volume. This is partly because of the contribution from additional pathologies such as leukoariosis, but also because of the importance of location which is much more important. For example, some locations, such as the thalami, can produce dementia with tiny lesions. Clinically silent infarcts also contribute to cognitive decline.

### SUBCORTICAL VASCULAR DEMENTIA

The histopathology in advanced subcortical VaD is characteristic. The only typical gross external abnormality is slight gyral atrophy. Hydrocephalus ex vacuo is seen on sectioning. Discrete lacunae are seen in 93% of cases, typically in the centrum semiovale, internal capsule, and basal ganglia. Confluent areas of leukoariosis occur separately from the infarcts and are commonly occipital, periventricular, and sometimes frontal, but the changes are primarily in the centrum semiovale and around the ventricles. The corpus callosum may be thinned but not ischaemic. In affected areas



**Figure 3** Lipohyalinosis. The walls of these small arteries are thickened, and their architecture replaced by eosinophilic deposit (medium power, H&E). Figure courtesy of Dr DG Munoz.

the pathology is variable. The earliest changes are of swollen myelin sheaths and oligodendrocytes. Subsequently incomplete demyelination and loss of oligodendrocytes develop followed by fragmentation of axis cylinders. Axons may be relatively preserved, resulting in a not uncommon mismatch between cognitive status and imaging findings. Rarefaction and cavitation with scattered microcystic areas of infarction follow. Gliosis is invariable. Subcortical association fibres are characteristically spared from direct lesions, but axons in the white matter remote from the lesions are reduced in number, presumably by wallerian degeneration. Atheromatous changes at the base of the brain occur in up to 93%, but are not severe enough to cause haemodynamic change. Carotid disease may also coexist. Cortical infarcts occur in up to one third but are not universally found and simply represent other manifestations of vascular disease. The arterioles supplying the deep white matter exhibit lipohyalinosis with perivascular lymphocytes, thickened walls and basal lamina, increased deposition of normal collagen, some of which is type I which is not seen normally, deposition of type IV collagen in the adventitia which is also not seen normally, disruption of the media, narrowed lumina, splitting of the internal elastic lamina, and some occluded vessels but often an intact endothelium, although the endothelial cells may be swollen (fig 3). Some vessels show hypertrophy of smooth muscle cells and others, where fibrosis has occurred, show a decrease.

### NEURAL NETS

Lesions interact synergistically and the study of neural nets in cognition provides some clues as to why this may be. In a neural net, loss of one set of connections can initially be circumvented by the use of other circuits, which may be slower and less efficient but may improve with use (learning). Thus initial ischaemic damage, particularly in the white matter, may not leave detectable deficits. However, the scope for recovery after further lesions decreases and lesions late in the disease process may cause disproportionate damage because their loss removes both their normal functions plus additional functions acquired as part of the recovery process after earlier events. Thus neural nets provide scope for recovery after lesions, but as the number of lesions increases this scope decreases, the sequelae of each successive lesion thus increasing. Neural nets also give clues to the

probable order of cognitive decline produced by multiple lesions which would initially affect the systems most dependent on complex neural nets. This explains why frontal involvement is one of the most prominent. Memory, which also depends on an extensive neural net, may also be affected relatively early, but not most prominently. However, in cases where the basis of the VaD was not multiple small lesions, this would not hold true and the pattern of cognitive loss would be much more closely linked to the precise site of the lesion. Even so, patients with right sided lesions exhibit impairment in verbal IQ and patients with left sided lesions exhibit impairment in performance IQ. This clearly shows the importance of generalised cognitive processing, presumably based on neural nets, as opposed to the more traditional localisation of function. Some support for the role of neural nets in global cognitive decline after stroke comes from factorial analyses of neuropsychological deficits after stroke. These show that a relatively small number of factors, distinct from the traditionally recognised cognitive domains, may form a mechanism by which dementia could occur on the basis of multiple infarcts. The factors may reflect neural nets. Further support comes from positron emission tomography (PET) and single photon emission computed tomography (SPECT), which show extensive diaschisis extending to the contralateral hemisphere, after a variety of small and large lesions, and also show remote cortical abnormalities in benzodiazepine receptors. These demonstrate functional disconnection and so might indicate the more important projections of the affected neural nets. Intuitively, sequential deficits closely spaced in time should leave a more severe deficit than the same lesions spaced far enough apart for complete recovery between lesions, but this hypothesis remains untested.

### CEREBRAL BLOOD FLOW AND METABOLISM

The old concept of arteriosclerosis was laid to rest by early PET studies of cerebral blood flow (CBF) which failed to demonstrate chronic cerebral ischaemia. Instead, they showed a modest fall in CBF in VaD, which was accompanied by a normal oxygen extraction ratio. Thus, CBF is matched to (decreased) metabolic demands, as is normal.

Within the deep white matter, stable xenon enhanced CT shows that CBF is decreased to a similar degree in both AD and VaD. This has been used to suggest chronic ischaemia as an aetiological mechanism for leukoaraiosis but PET does not support this. Once again, PET does not show ischaemic changes at rest. However, there does appear to be diminished perfusion reserve and when such patients are given acetazolamide, a vasodilator, they do not exhibit the normal increase in regional CBF. If this is to be translated into a pathophysiological mechanism, it has to be postulated that patients undergo periodic hypotension causing ischaemia in the zones of decreased perfusion reserve. There is evidence for a greater predisposition to postural hypotension in patients with subcortical VaD as well as an association with greater blood pressure variability.

### DIFFERENTIAL DIAGNOSIS

The principal differential diagnoses are from AD and depression supervening on stroke, as depression commonly follows stroke. In 90% of cases where multiple infarcts are present there is also a history of stroke or of transient ischaemic attacks. However, in cases where leukoaraiosis alone is the vascular pathology, a history of stroke may be

absent in up to 40% and focal signs are also less common. The use of the ischaemic scale score (table 1), classifying those with a score of 4 or less as Alzheimer's and those of 7 or more as VaD, has 89% sensitivity and specificity, but distinguishing mixed dementia from either VaD or AD remains difficult with poor specificity. The use of CT to identify infarcts increases diagnostic accuracy. Compounding the difficulty of identifying VaD is its common coexistence with AD and the important effect of cerebrovascular disease in hastening the clinical manifestation of AD in what are, in effect, mixed cases, even though there may be no specific history of stroke and the vascular disease may amount to only microinfarcts. Furthermore, many previous studies concerning the diagnosis of AD have dismissed small volumes of ischaemic damage; in view of the interaction between cerebrovascular disease and AD this now seems highly inappropriate and about one quarter of cases of clinically diagnosed "pure" AD will have some vascular component.

Of at least equal importance to the identification of VaD itself is identification of the cause of the vascular events, since the treatment and prognosis depend on the cause. The remainder of the differential diagnosis is that of dementia.

Conditions that may be confused with subcortical VCI on both clinical and neuroimaging grounds are relatively few. Normal pressure hydrocephalus is the most important of these as its classical presenting triad may resemble subcortical VCI. It may occur in the same age group and periventricular white matter changes will be seen in both conditions, but the pattern of the white matter changes may differ with deep white matter changes in the subcortical VaD group. Depression in association with stroke should always be sought as depression is a common, treatable, and often neglected differential diagnosis as well as being a common complication of subcortical cerebrovascular disease. It should also be emphasised that depression is very common after stroke, regardless of stroke severity. Hereditary multi-infarct dementia (CADASIL) can be recognised by the young age of onset, the coexistence of migraine, the absence of hypertension, and the family history (if available), but the clinical features may otherwise closely resemble subcortical VaD. The gait abnormality of subcortical VCI may be confused with extrapyramidal disease, particularly striatonigral degeneration, but focal signs and white matter changes on imaging should distinguish them. Cerebral vasculitis may cause a rapidly progressive dementia, usually rather faster than subcortical VaD; it is accompanied by focal neurologic changes and white matter changes in neuroimaging, and should be borne in mind as a rare alternative.

A variety of other conditions may cause similar white matter changes on imaging but should be readily distinguishable from subcortical VaD on other criteria (table 2).

### CADASIL AND RELATED CONDITIONS

An hereditary multi-infarct dementia consistent with "cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy" (CADASIL) was first described 30 years ago; it was subsequently described in more detail and its cause localised to chromosome 19 in the early 1990s. It occurs in all racial groups and its prevalence may be of the order of 1:100 000.

It is caused by mutation of the notch 3 gene, which codes for a large transmembrane receptor. The gene is expressed in vascular smooth muscle cells in a variety of organs and mutated genes cause accumulation of the extracellular

**Table 2** Differential diagnosis of subcortical vascular cognitive impairment

- ▶ Acute disseminated encephalomyelitis
- ▶ Alzheimer's disease
- ▶ CADASIL
- ▶ Carbon monoxide poisoning
- ▶ Cerebral vasculitis
- ▶ Creutzfeldt-Jakob disease
- ▶ Depression
- ▶ Frontotemporal dementia
- ▶ Gangliosidoses
- ▶ Hepatic failure
- ▶ HIV dementia
- ▶ Hypertensive encephalopathy
- ▶ Leucodystrophies
- ▶ Metabolic disease
- ▶ Methotrexate leucoencephalopathy
- ▶ Mucopolysaccharidoses
- ▶ Multiple sclerosis
- ▶ Normal-pressure hydrocephalus
- ▶ Parkinson's disease
- ▶ Progressive multifocal leucoencephalopathy
- ▶ Radiation encephalopathy
- ▶ Renal failure
- ▶ Subacute sclerosing panencephalitis

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

portion of the receptor within blood vessel walls. This material was originally noted to be PAS positive on light microscopy and on electron microscopy is seen as a granular osmiophilic deposit (GOM) within vessel walls adjacent to smooth muscle cells. These changes may be seen in a variety of tissues but it is in the brain that the pathology gives rise to clinically apparent disease. This seems to be due primarily to mechanical damage to the walls of small arteries (below 400  $\mu\text{m}$ ), arterioles, and capillaries. Most of the damage is ischaemic with multiple lacunar infarcts and other areas of leukoaraiosis, but haemorrhage has been reported.

The clinical presentation is most characteristically in the fourth decade with recurrent transient ischaemic attacks (TIAs) or strokes, but clinical onset as late as the seventh decade has been reported. Migraine, usually with aura, develops in half of cases, usually a few years before the first vascular events. This may be preceded by a decade by psychiatric manifestations, most commonly depression, in a substantial minority. Epilepsy occurs but is uncommon. The disease progresses initially with recurrent vascular events with recovery, but as disability increases these discrete events gradually merge and the condition becomes gradually progressive. As might be expected with extensive small vessel disease, the picture is typically pseudobulbar with extrapyramidal features in those where the disease involves the basal ganglia. At this stage subcortical cognitive impairment may be seen and this can proceed to frank dementia, but presentation with dementia is unusual. About 10% of cases may present with an acute encephalopathy preceded by migraine and characterised by headache, confusion, pyrexia, and fitting resolving fully over 7–14 days.

In the majority of patients, the condition may be suspected with the development of otherwise unexplained small vessel cerebrovascular disease at a young age and without vascular risk factors, although in those patients with later presentations, coincidental vascular risk factors may be present. An

accompanying history of migraine with aura and psychiatric illnesses supports the diagnosis, as does a family history, although new mutations have been reported and the family history may be limited by misdiagnoses in the relatives. Additional evidence for the diagnosis may be apparent on MRI. The bulk of the changes caused by CADASIL are identical to those seen in the common forms of small vessel disease. However, these common forms affect the deep perforating arteries and so tend to spare the external capsule, corpus callosum, and anterior temporal lobe; this pattern is not seen in CADASIL and ischaemic white matter lesions at these sites support the diagnosis (fig 4). Angiography should be avoided; the vessels affected in CADASIL are smaller than those visible on angiography which is therefore characteristically normal, and up to two thirds of patients may suffer neurological complications which can be permanent.

The diagnosis can be confirmed by genetic analysis in the majority of cases. However, there are over 30 mutations and the notch 3 gene is large; it is not practical in routine diagnostic work to test the whole gene, but the mutations do cluster which facilitates the development of screening protocols. These will generally identify about two thirds of cases. As the disease affects vessels in many organs a peripheral biopsy can often be positive. Skin has often been used but may be false negative in almost half of cases. Muscle may be better as the sensitivity of the test is related to the number of smooth muscle cells in arteriolar walls, and these are more numerous in muscle (and nerve) than skin. Routine laboratory testing therefore comprises genetic screening and electron microscopy of a suitable biopsy with further genetic analysis where the biopsy confirms GOM.

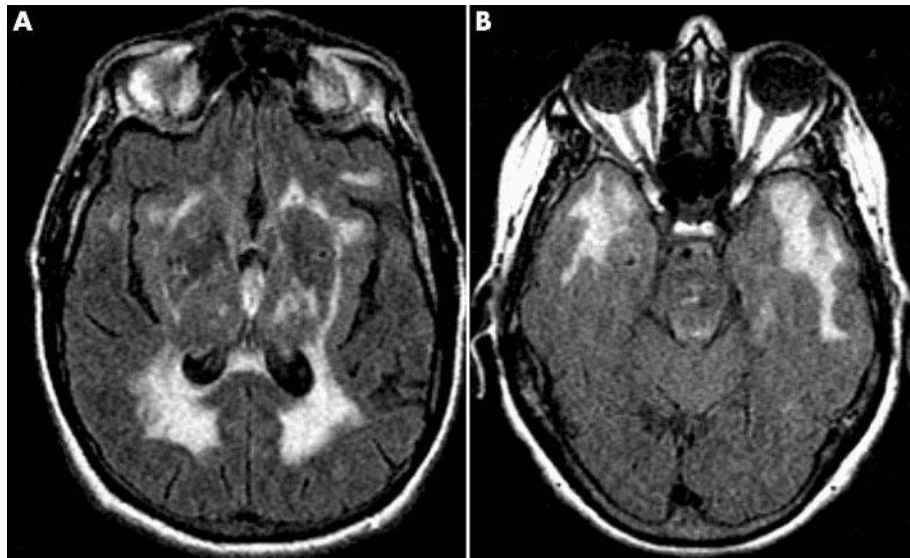
While CADASIL is the best described single gene condition affecting vessels in this way, it is not the only one. One of the reference laboratories studying CADASIL has reported that only a third of skin biopsies are positive for GOM, but that many of the others exhibit pathological changes in the vessel walls which they felt could be divided into eight groups, some of which ran in families. The Japanese literature contains a number of reports of a condition with subcortical infarcts and leucoencephalopathy with an autosomal recessive pattern of inheritance (sometimes termed CARASIL), often accompanied by degenerative disease in the lumbar spine and knees and alopecia. A family has been reported from Hamburg with a condition resembling CADASIL but without GOM. There may, therefore, be several as yet poorly characterised inherited diseases of small vessels affecting the cerebral circulation.

### POST-STROKE DEMENTIA

Dementia after stroke is now increasingly recognised. Initial studies suggested that 30% of all stroke patients were demented three months after stroke, but that 10% were demented before the index stroke. It now appears that these high figures arose because of case selection. In the Framingham study, the 10 year risk of post-stroke dementia was rather lower at 19.3% of cases and dementia developed in 11% of controls, suggesting that the risk attributable to an index stroke is lower than had been thought.

Even in those without prior dementia, post-stroke dementia correlates with pre-stroke cognitive status suggesting pre-existing pathology in at least some cases. This is supported by the finding that MRI changes more usually associated with degenerative dementia correlate with pre-stroke cognitive decline. Pre-existent disease may also be vascular, cognitive





**Figure 4** MRI in CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy). Characteristic MRI finding in CADASIL with involvement of the external capsule and anterior temporal lobes. Figures courtesy of Professor HS Markus.

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decline after stroke being much more common in those who have small vessel cerebrovascular disease. Blacks may be at greater risk of post-stroke dementia than whites.

The risk of dementia after stroke increases with age, from 15% in those aged 60–69 years to 52% for those over 80. Over a third of these have mixed dementia. Cognitive impairment short of dementia is found in another 10% of those over 55 post-stroke when scored using the insensitive mini mental state examination (MMSE). The true proportion will be appreciably higher. The incidence of cognitive impairment after stroke sufficient to adversely affect outcome but not meeting current criteria for VaD is as high as 35.2%, compared to 3.8% with a similar degree of impairment in stroke-free controls.

While post-stroke dementia has been the subject of a number of publications recently, it is important to realise that it is not a specific entity. Rather, it reflects the interactions of pre-existing and subsequently evolving cognitive damage, both degenerative and vascular, about a timed further event—that is, a symptomatic stroke.

### MIXED DEMENTIA

Alzheimer's original work on his eponymous disease mentions arteriosclerosis, endothelial proliferation, and neovascularisation, suggesting that the earliest reports of AD may have had a vascular component to them. This was largely forgotten for most of the 20th century and during the resurgence of AD there was a tendency to simply ignore coexistent cerebrovascular disease. Roth, in 1971, first suggested that "There is evidence that the two types of pathological change augment one another to a statistically significant degree in the production of dementia". This was, again, largely ignored. Despite this, a variety of early necropsy studies suggested that up to 44% of cases of dementia were mixed. The Nun study was the first to quantify the interaction of vascular and AD pathologies, demonstrating that in those who met criteria for AD the average MMSE score before death was 8 in those with infarcts and 17 in those without, and that the MMSE decreased by 0.8/tangle in those with infarcts and 3/tangle in those without. The Medical Research Council cognitive function and ageing study (CFAS) group went on to show that, when properly

sought, 81% of those with dementia has ischaemic lesions at necropsy although almost half met criteria for AD.

There is now considerable interest into whether AD and VCI are more than coexistent unrelated conditions. There is some evidence to suggest that they share risk factors although the quality of this evidence is limited by case identification. As standard criteria for AD do not rigorously exclude cases with coexistent cerebrovascular disease, and as the two commonly coexist, it is self evident that many patients with mixed disease will be diagnosed as having Alzheimer's. Consequently, it may be that vascular risk factors are seen in AD by error and that if case selection was rigorous, vascular risk factors would not be seen in truly pure AD. The one circumstance through which there is a clear shared pathology is amyloid although, even here, the amyloid of AD is cortical whereas the most common vascular pathology is subcortical and this association may be of little consequence.

In practice, it is crucial not to make diagnoses of "pure" AD unless there is no evidence of cerebrovascular disease at all—that is, a good quality MRI without any infarcts or leukoaraiosis. In all others, a diagnosis of mixed disease should be considered and attention given to meticulous control of vascular risk factors, this being the only intervention that stands any chance of slowing progression.

### INVESTIGATION

Cognitive impairment can be established by history and examination alone. An assessment for depression should be included in the examination. Imaging is required to confirm the presence of cerebrovascular disease and to exclude other structural causes. CT may be sufficient in advanced cases when infarcts and extensive leukoaraiosis will be readily appreciated, but in earlier VCI MRI is preferred as it will better show leukoaraiosis and may be essential if certain conditions such as CADASIL are suspected.

The vascular component of the investigations should be directed by clinical suspicion but should not be neglected as the identification and treatment of vascular risk factors is one of the major aspects of management. Not all investigations are routinely required. However, a full blood count, erythrocyte sedimentation rate, glucose, and electrocardiogram

## Abbreviations

- ▶ **AD:** Alzheimer's disease
- ▶ **ADAS-Cog:** Alzheimer's disease assessment scale, cognitive subscale
- ▶ **CADASIL:** cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy
- ▶ **CBF:** cerebral blood flow
- ▶ **CGI-C:** clinical global impression of change
- ▶ **CSF:** cerebrospinal fluid
- ▶ **CT:** computed tomography
- ▶ **DSM-IV:** *Diagnostic and statistical manual of mental disorders*, 4th ed
- ▶ **ECG:** electrocardiogram
- ▶ **EEG:** electroencephalogram
- ▶ **GOM:** granular osmiophilic deposit
- ▶ **HIV:** human immunodeficiency virus
- ▶ **ICD-10:** International classification of diseases, version 10
- ▶ **MID:** multi-infarct dementia
- ▶ **MMSE:** mini mental state examination
- ▶ **MRI:** magnetic resonance imaging
- ▶ **NINDS-AIREN:** Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et L'Enseignement en Neurosciences (AIREN)
- ▶ **PET:** positron emission tomography
- ▶ **SPECT:** single photon emission computed tomography
- ▶ **TIA:** transient ischaemic attack
- ▶ **VaD:** vascular dementia
- ▶ **VCI:** vascular cognitive impairment

(ECG) should be done. Where appropriate, syphilis and HIV serology, carotid duplex Doppler, chest x ray, echocardiography, Holter monitoring, thrombophilia screen, lipid profile, lupus anticoagulant, anticardiolipin antibodies, and autoantibody screen are justifiable. Thyroid function, vitamin B12, and red cell folate are mandatory. A glycosylated haemoglobin may detect unsuspected diabetes. Cerebral angiography is indicated if carotid surgery is considered, or to demonstrate beading of the smaller cerebral vessels if a cerebral vasculitis is suspected, but it is not a routine investigation and can in any case miss an active vasculitis. CSF examination is rarely required except where an infectious or inflammatory aetiology is possible and where normal pressure hydrocephalus is possible, as this is a not uncommon differential of subcortical VCI, with which it may coexist, and a clear response to CSF drainage can be helpful. Dural or brain biopsy may be needed in those rare cases vasculitis is a likely explanation. EEG is rarely helpful and functional imaging is not confirmed as sufficiently reliable as a diagnostic tool.

## MANAGEMENT

### Symptomatic treatment

Since 2002 five large randomised studies of the symptomatic treatment of probable and possible VaD have been published comprising two studies of the anticholinesterase donepezil in VaD, two studies of the NMDA receptor antagonist memantine in mild to moderate VaD, and a study of the anticholinesterase galantamine in "probable VaD and AD combined with cerebrovascular disease". These few studies exceed in quantity and quality everything that has been published before.

While these findings are exciting and represent new developments, there are a number of cautions. The first is the relatively modest benefits seen in all these trials. For the

anticholinesterases, the benefit on the Alzheimer's disease assessment scale, cognitive subscale (ADAS-Cog) amounts to about 3 points and to less than 1 point on the MMSE. While statistically significant, these effects are so slight that they may not be useful routine treatments—perhaps treatments that should be tried in all but maintained only in individual responders.

These drugs were originally developed for Alzheimer's disease on the basis of the cholinergic hypothesis; much has been made of the presence of a cholinergic deficit in vascular dementia, which probably occurs because of ischaemic damage to the cholinergic projections, but this is proportionately considerably less than is seen in Alzheimer's disease. Indeed, the presence of a cholinergic deficit is not required for the anticholinesterases to produce cognitive improvement, which can be seen in airline pilots and university students, and so the cholinergic hypothesis is neither necessary nor sufficient to explain the modest benefits.

Memantine has slightly less effect than the anticholinesterases on the ADAS-Cog, perhaps a better effect (2 points) on the MMSE, but no detectable effect on the clinical global impression of change (CGI-C), while its side effects are very close to placebo level.

There is a further question as to what is actually being treated in these patients. The NINDS-AIREN criteria were used in these trials. They have been extensively criticised in several respects, but the relevant fault here is their Alzheimer based origin. While the criteria produce a population different from that obtained by pure Alzheimer criteria, such as NINCDS-ADRDA, as witnessed by the almost universal lack of progression in the control groups in VaD studies, it is noteworthy that in the galantamine study, where mixed dementia was recognised, the benefit of treatment was confined to those with mixed disease, supporting the notion that the bulk of the effect is on the Alzheimer component.

The typical apraxic gait of subcortical VaD is not normally amenable to treatment but, where the burden of vascular disease lies in the basal ganglia or substantia nigra, levodopa can be helpful.

Depression is common in association with stroke and subcortical cerebrovascular disease, the cognitive consequences of which it may closely mimic. If there is any suggestion of depression as a contributory factor, a course of treatment with antidepressant medication is usually justifiable and should be tried first as a positive response is likely to be both more rapid in onset and greater in magnitude than with any other drug.

### Prevention and slowing of progression

As might be expected, it is modification of vascular risk factors that may prevent, slow or arrest the progression of VCI. However, data pertaining to cognition are few and in part this may be because many of the historically well established risk factors were identified in trials in which cognition was not an outcome variable. Nonetheless, it should be remembered that lack of evidence of efficacy is not the same as evidence of lack of efficacy! There are some data that directly address cognition derived from more recent studies. The Syst-Eur study demonstrated that a reduction of 7 mm Hg in systolic and 3.2 mm Hg in diastolic blood pressure over 3.9 years halved incident dementia. The absolute figures are a little less impressive at 3 cases per 100 patient years. The PROGRESS study demonstrated a non-significant reduction, over 3.9 years of follow up, in risk of



dementia from 7.1% to 6.3% but a significant reduction in cognitive decline from 11% to 9.1%, this benefit being attributable to the prevention of recurrent stroke. The study used the MMSE to rate cognition and the DSM-IV to diagnose dementia. Both of these are optimised for AD and it may well be that the benefits of treatment would have been greater had the methodology been optimised for VCI.

The evidence for benefit from the statins is weaker. The PROSPER study followed 6000 individuals aged 70-82 for 3.2 years, half of them randomised to receive pravastatin, and was unable to demonstrate any benefit on stroke, cognition, or activities of daily living despite showing a benefit on myocardial infarction and TIA. Several cognitive rating scales were used here including the Stroop, which is sensitive to subcortical disease, and it is unlikely that the study was artefactually negative through use of inappropriate tests of cognition. In a four year observational study of 1000 post-menopausal women, statin users had a trivially (1%) higher score on a modified MMSE.

Given the established benefits of the statins in preventing adverse vascular events, the discrepancy between these and antihypertensive treatment requires some explanation. This may lie in the fact that subcortical vascular dementia is the single most common form of vascular dementia and that hypertension is, by a very considerable margin, the most powerful treatable risk factor. Cholesterol has little association with small vessel disease and the plaque stabilising, antioxidant and other properties attributed to the statins may not be relevant to lipohyalinosis and so to small vessel disease.

The general points made concerning the management of VaD probably apply substantially to subcortical VaD, but few trials have been done in patients specifically limited to subcortical VaD and not all the recommendations for VaD are relevant. The strong association between subcortical VaD and hypertension suggests that control of hypertension may be particularly important in preventing progression. However, treatment should be started cautiously. Chronically hypertensive patients have an autoregulatory range for cerebral blood flow shifted to accommodate higher perfusion pressures. Even with treatment this will not fully return to normal. They are thus readily susceptible to hypotension, even at pressures that would otherwise be considered normal. This may be important, as periodic hypotension is a suggested mechanism for the white matter changes seen in these patients. Cerebral vasomotor reactivity may improve by treatment with pravastatin in patients with subcortical small vessel disease, but whether this has cognitive benefits is as yet unknown. Nimodipine may have some effect to slow progression in subcortical VaD but not in other kinds of VaD.

## PROGNOSIS

The prognosis of VaD varies considerably according to the criteria used to make the diagnosis. As a result, data vary from VaD being stable in the medium term in that the placebo groups of several studies of treatment in VaD have shown no progression, to other work suggesting MID shortens life expectancy to about 50% of normal at four years from initial evaluation. Females and those with higher education do better. In the very elderly, three year mortality may reach two thirds, almost three times that of controls. In one study, the six year survival rate was only 11.9%, about a quarter of that expected, though many of these patients were elderly and severely demented at entry. About a third die from complications of the dementia itself, one third from

cerebrovascular disease, 8% from other cardiovascular disease, and the rest from miscellaneous causes. Overall, the effect of VaD on mortality is similar to that of AD.

The presence of VCI predicts the subsequent development of frank dementia. In a Japanese study, VCI increased the likelihood of subsequent dementia over the next decade from 8% to 42%, while in the Canadian study of health and aging, approximately half were dead and half institutionalised after five years. However, in 16% there was no cognitive decline, or even improvement, reflecting the diversity of potential outcomes in this condition.

## CONCLUSIONS

The old concepts of vascular dementia and Binswanger's disease, along with their criteria, are dead but their replacements, VCI and its subcortical VCI, do not yet have criteria. However, criteria are intended mainly for research purposes and the clinician is encouraged vigorously to hunt out these conditions and deal with their risk factors. It is sufficient to identify vascular risk factors, the slightest of cognitive loss, and evidence, however minimal, of cerebrovascular end organ damage, to formulate a working diagnosis of VCI and to commence risk factor modification. The goal is not to diagnose dementia, it is to prevent it. The increasing awareness of mixed dementia dictates that even where the diagnosis is thought to be primarily AD, that evidence of coexistent cerebrovascular disease and its risk factors be sought and these dealt with too, not least because there is no other treatment that can slow the progression of the disease. Depression must always be sought and treated; it is a common complication of cerebrovascular disease and mimics subcortical VCI. Treatment of this is far more likely to produce symptomatic improvement than the anticholinesterases or memantine, the efficacies of which are marginal.

## RECOMMENDED READING

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