Vascular dementia

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Abstract

Vascular disease is the most common treatable cause of dementia. Contemporary epidemiological models suggest that in developed Western societies, vascular disease alone accounts for about 15% of all dementia. In association with Alzheimer's disease, however, it is suspected to be involved in at least 50% of all dementia. Recent research points to shared risk factors in vascular dementia and Alzheimer's disease, and common pathogenetic processes are likely.

The exact criteria required for a diagnosis of vascular dementia remain imprecise and poorly developed. Advances in brain structural and functional imaging provide the best prospects for improvement in vascular dementia diagnosis.

Here we set out the major processes that impinge upon the health of neurones and may contribute to vascular dementia. Clinical trials of interventions that might slow progression of cognitive impairment to vascular dementia are fully justified and are likely to improve the care of many old people at particular risk of dementia.

Key words: vascular dementia, diagnosis, brain imaging, epidemiology, ageing, risk factors.

Br J Cardiol (Heart Brain) 2003;**10**:HB 8–HB 14

Introduction

Progress in understanding pathogenetic processes in vascular disease is directly relevant to the problem of age-related dementia. Typically, disorders like Alzheimer's disease, Huntington's disease and Parkinson's disease are considered to form distinct diagnostic entities, each with their own separate causes, courses and potentially quite separate molecular pathologies.[1] In contrast, vascular dementia has been regarded as much more amorphous. It is often without precise boundaries and (with rare exceptions) is distributed unevenly in the brain, with neurological and cognitive symptoms and signs seeming to arise in late life almost by the dictates of chance.

In the past decade, genes causing rare familial forms of these neurodegenerative diseases have been identified, molecular pathologies comprehensively described and specific treatments aimed at these pathways have entered clinical trials.[1] Similar advances have not, though, taken place in vascular dementia: this group of disorders seem to have been forgotten and undervalued. Such neglect consolidated the classical model of distinct neurodegenerative disorders on the one hand and disorders of neural function attributable to vascular disease on the other. While this model certainly remains true for early-onset dementias – known genetic mutations account for almost 10% of cases[2] – it is much less valid for late-onset dementia. The boundaries are much less clear between late-onset Alzheimer's disease and vascular dementia, and between these two conditions and brain ageing in the absence of dementia.

In this article we summarise what is known of the epidemiology of vascular dementia and the related complex issue of diagnosis. We then address likely pathogenetic mechanisms, first by considering in general the principal influences on the health of neurones and then the specific mechanisms of neurotoxic effects of homocysteine. These considerations have important therapeutic and preventive implications, to which studies on stroke have made a partial but informative contribution.

Cognitive deficits in vascular dementia

Hachinski *et al*.[3] provided a classic description of the stepwise deterioration and fluctuating course of typical vascular dementia in 1974. Their clinical descriptions formed the basis of the Hachinski ischaemic score, which included abrupt onset, stepwise progression, fluctuating course, nocturnal confusion, relative preservation of personality, depression, somatic complaints, emotional incontinence, history of hypertension, history of strokes, evidence of associated atherosclerosis and focal neurological signs/symptoms. Their descriptions were based on a series of patients with multiple large cortical infarcts (multi-infarct dementia). This is now seen to be a relatively uncommon variant of vascular dementia.[4]

The more modern, broad concept of vascular dementia includes patients who do not conform with the classical description and for whom specific cognitive deficits in attention, concentration and executive function are more important. Memory

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Figure 1. FLAIR axial MR images of multiple cortical infarcts in the frontal, parietal (**a**) and occipital (**b**) lobes

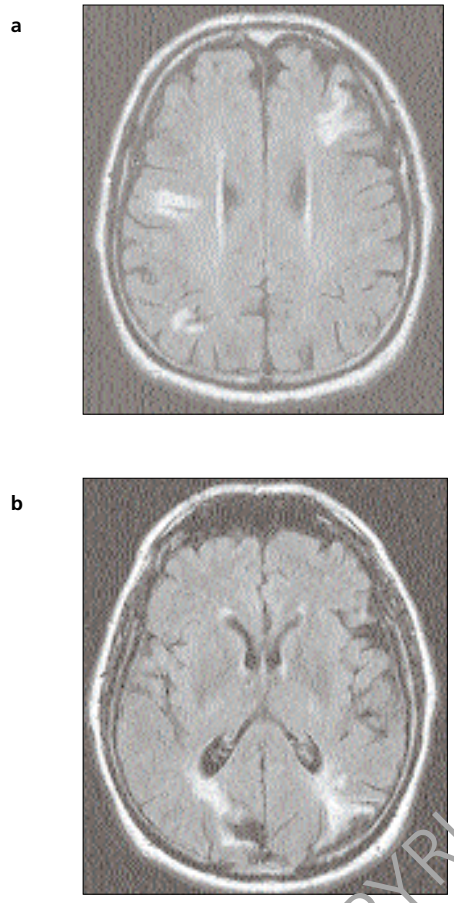
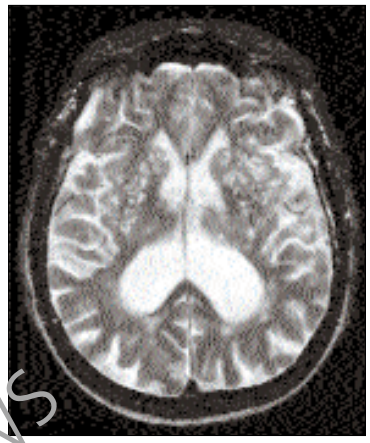


Figure 2. T2W axial MRI showing multiple lacunar infarcts in the caudate, putamen and globus pallidus bilaterally. There are white matter hyperintensities adjacent to the trigones of the lateral ventricles



impairment, a prominent feature in Alzheimer's disease, is a far less typical presenting symptom of vascular dementia. At the bedside, individuals with vascular dementia perform less well in tests of verbal fluency and show greater deficits in executive functions. Contrary to expectations, clinical studies of differences between vascular dementia and Alzheimer patients do not reveal characteristic deficits in language or visual spatial ability.

To remedy diagnostic deficits, several sets of diagnostic criteria have been proposed. Both ICD-10[5] and DSM-1V[6] criteria require the presence of cerebrovascular disease for a diagnosis of vascular dementia. Further, this disease must be judged to be related causally to the dementia. The criteria suffer from the important weakness that no guidance is given on interpretation of the neurological examination or brain imaging results.

Definition of vascular dementia

Traditionally, the diagnosis of vascular dementia was made by diagnosing dementia according to Alzheimer's disease type criteria, of which memory impairment is a core feature. On to this picture ischaemic vascular events are superimposed, giving rise to a stepwise cognitive decline.[7] However, it is now recognised that vascular dementia does not follow the typical onset or pattern of progression of Alzheimer's disease and that cognitive impairment due to vascular disease may present as a continuous decline without superimposed stroke-like episodes. There is also a desire to detect vascular cognitive impairment at an earlier stage than the current definition of vascular dementia. The hope is that earlier detection might allow modification of risk factors to influence outcome. Such a definition of vascular cognitive impairment must be evidence- rather than consensus-based.[8] It is also recognised that vascular cognitive impairment/dementia co-exists with other forms of dementia and that, if mixed dementias are included, vascular dementia may be the commonest type of dementia in the elderly.[9]

The concept of vascular dementia has gradually evolved to take on a more precise form than that intended in the original neuropathological descriptions. Currently, many types of pathophysiological mechanism that impair cerebral blood supply and lead to various types of cerebral vascular pathology are included in the spectrum 'vascular dementia'. Neuropathological changes include multiple cortical infarcts; a single infarct affecting a brain structure critical for memory (sometimes called 'strategic' or 'bottleneck' infarct); small vessel disease which features lacunar infarcts; and multiple ischaemic white matter lesions distributed widely throughout subcortical structures. Haemorrhagic dementias are relatively uncommon, and mixed pictures are the rule rather than the exception. These neuropathological features define vascular dementia but do not establish clear boundaries between what is vascular dementia and what is not, or between subtypes of vascular dementia. These problems of definition have caused considerable inconsistency in clinical descriptions of patients with presumed vascular dementia and have placed important constraints on research progress.

Figure 3. The cerebral reserve hypothesis of cognitive ageing is shown schematically. Here, the trajectory of cognitive ageing in the absence of dementia is shown as an unbroken line. The broken line crosses a hypothetical threshold of cognitive reserve, after which the symptoms of dementia ('decompensation') appear. The term 'load' is used to summarise the diverse burdens of age-related brain pathology which impair cognitive function. Vascular pathology is the most frequently encountered source of this type of burden

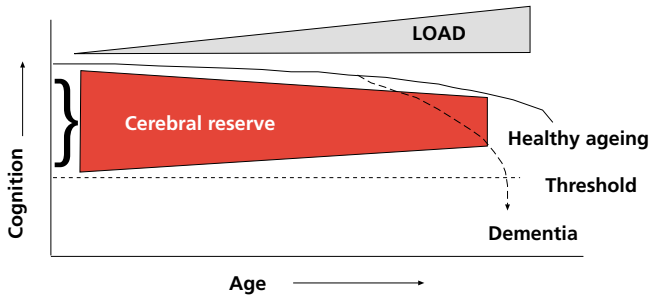
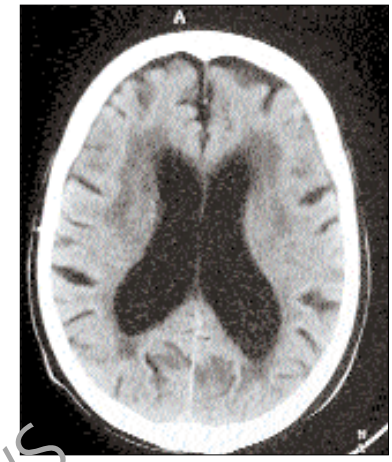


Figure 4. CT showing reduced attenuation in the frontal and periventricular white matter



Neuropathology

Multi-infarct dementia is associated with multiple cortical infarcts in different arterial territories (figure 1 a and b). However, subcortical white matter small vessel disease is more prevalent and accounts for a greater burden of vascular cognitive impairment than multi-infarct dementia.[4] The changes associated with white matter ischaemic lesions were characterised by Fazekas in 1993, with grade II and III lesions representing focal areas of arteriosclerosis, demyelination and astrogliosis, progressing to frank infarction.[10] Small vessel disease is also associated with tiny lacunar infarcts in the basal ganglia (figure 2). Such white matter ischaemic changes and lacunar infarcts are most obvious in the frontal lobes and may explain cognitive deficits, possibly attributable to disconnection between cortical areas.

Persistent pervasive memory impairment attributable to damage to cortical association areas and to tissue in or around the hippocampus dominates the clinical features of vascular dementia. Of course, this location is unsurprising as the presence of memory impairment is central to the diagnosis of dementia; moreover, the hippocampus and related cortical association areas are essential to memory. The extent of vascular lesions detected on neuroradiological examination is of more relevance to understanding the role of vascular pathology in cognitive impairment.

Much of the renewed interest in the pathophysiology of vascular neuropathology in age-related cognitive disorders derives from the concept of cerebral (or cognitive) reserve. This problem is illustrated as a graphical process of cognition against age with a vascular burden in figure 3. The concept of cerebral reserve was introduced to explain cognitive differences between individuals who appeared to suffer the same degree of neuropathological change but who differed markedly in cognitive impairment. Recent studies suggest that the extent of cerebrovascular pathology might explain part of the degree of difference, perhaps through some sort of summative mechanism that imposed a total burden on brain function that exceeded its compensatory capacity.

Brain imaging

Computed tomography (CT)

CT produces brain images that depend on attenuation of X-rays according to tissue density. Areas of established cortical infarction appear as low-density areas that approach that of cerebrospinal fluid extending to the brain surface, as the result of progressive gliosis. Lacunar infarcts appear the same and typically occur in the caudate, putamen, globus pallidus and thalamus. White matter ischaemic changes are seen as low density, patchy areas in the subcortical and periventricular white matter (figure 4), although magnetic resonance imaging (MRI) is a more sensitive modality for demonstrating these lesions. Such changes are often also seen in the brain stem, particularly in the anterior pons.

Magnetic resonance imaging (MRI)

This is the most sensitive structural imaging method for demonstrating white matter abnormalities. They appear as areas of increased brightness on T2, proton density and fluid attenuation inversion recovery (FLAIR) images. White matter lesions are seen as small punctate areas of increased signal that then coalesce to form extensive confluent areas of increased signal (figure 5). Periventricular abnormalities are thought to arise due to a different pathogenetic process and may be associated with altered cerebrospinal fluid dynamics or breaches in the ependymal lining of the ventricles. In severe cases periventricular abnormalities merge with deep white matter areas of high signal and become

Figure 5. T2W MRI showing white matter hyperintensities in the periventricular and deep white matter. There is also generalised atrophy

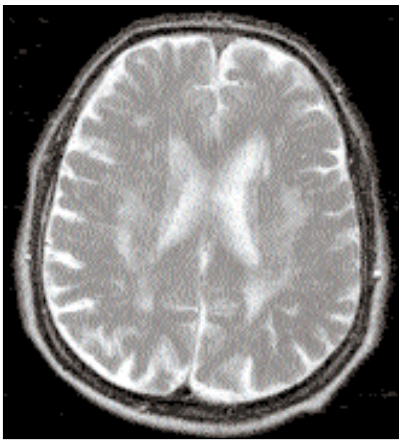
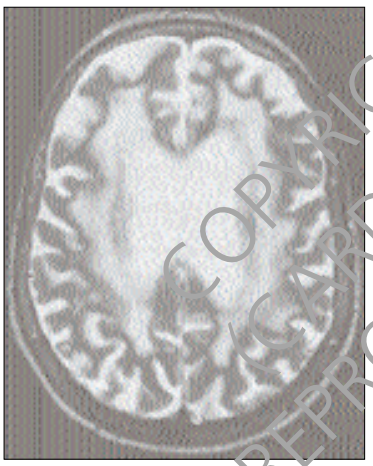


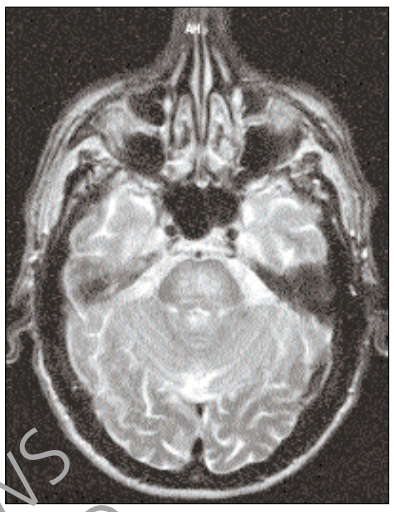
Figure 6. T2W MRI showing extensive white matter hyperintensities. Periventricular high signal merges with high signal in the deep and subcortical white matter



indistinguishable, giving rise to the typical appearance associated with 'Binswanger's encephalopathy' (figure 6).

Cortical infarcts appear as increased signal on T2-weighted images and low signal on T1-weighted images. In the acute phase they are swollen and will appear bright on diffusion-weighted images. As with CT, ischaemic changes in the brainstem are frequently observed. These are most obvious on T2-weighted images (figure 7) and are associated with clinical findings of impaired balance and gait.[11] Intracranial haemorrhage is most sensitively detected on T2* gradient echo images and will persist as a cleft of low signal on T2-weighted images as the result of intracellular haemosiderin.

Figure 7. T2W MRI showing white matter hyperintensities in the pons



Regional cerebral blood flow imaging with single photon emission computed tomography (rCBF SPECT)

rCBF SPECT is widely used in the imaging of dementia and cerebrovascular disease. The most commonly used agents are hexamethylpropyleneamineoxine (HMPAO) and ethylcysteine dimer (ECD), both of which are labelled with ^{99m}Tc. Most experience in the UK is with HMPAO. This agent is taken up on first-pass perfusion through the cerebral circulation and should be regarded as largely a grey matter imaging agent. Some 80% of the agent binds to grey matter. The resulting images are usually displayed on a colour scale and are very sensitive for alterations in cerebral perfusion.

It is often difficult to advise on the use of these techniques in the differential diagnosis of dementia as this choice will be influenced by local imaging availability and expertise. MRI provides the most sensitive structural information and reveals white matter ischaemic change, cortical and lacunar infarcts; it is also very sensitive in detection of haemorrhage. The Royal College of Psychiatrists currently recommends CT as a first-line investigation in dementia. CT will exclude significant structural abnormalities but is less sensitive than MRI for white matter ischaemic change. Although the diagnosis of dementia can only be made on clinical grounds, the appearances on rCBF SPECT are useful to distinguish between the posterior temporoparietal defects of Alzheimer's disease (figure 8) and the multiple patchy perfusion defects associated with cerebrovascular disease (figure 9).[12] In some cases of vascular dementia patchy perfusion defects are seen, with a more generalised reduction in one or more vascular territories (figure 10). In some cases the pattern of defects seen on imaging may be mixed, reflecting the prevalence of mixed Alzheimer's/vascular dementia in elderly subjects.

Vascular disease and cognitive ageing

The health of neurones is affected by three basic processes, as reviewed by Cotman.[13] These are apoptosis (programmed cell

Figure 8. ^{99m}Tc HMPAO SPECT in Alzheimer's disease. There are posterior temporoparietal perfusion defects

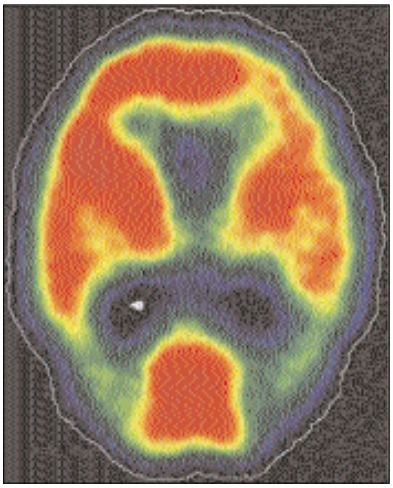


Figure 9. ^{99m}Tc HMPAO SPECT in vascular dementia. There are multiple focal perfusion defects

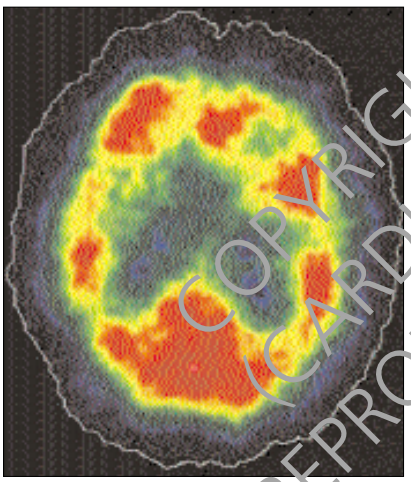
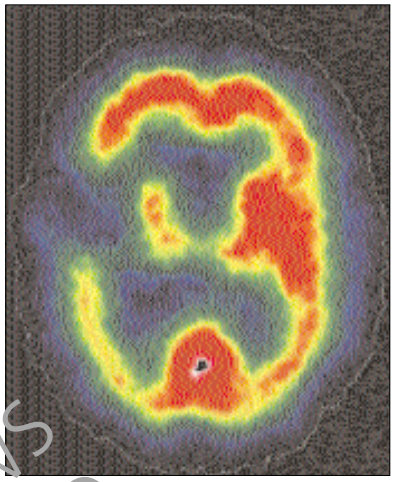


Figure 10. ^{99m}Tc HMPAO SPECT in a patient with generally reduced perfusion in the right middle cerebral arterial territory, including the basal ganglia



death), inflammation (acute phase injury) and the generation of free radicals (oxidative stress). Although all three processes are important in the maintenance of healthy neurones, they are also implicated in both dementia and age-related cognitive decline. In the ageing brain, a delicate balance is achieved between the brain's requirements and the effects of chronic, unwanted activation of any one or more of these three processes. For example, apoptosis is fundamental to the removal of abnormal neurones or glia, is involved in synaptic turnover and remodelling and plays a central part in the brain's compensatory response to age-related damage. Inflammatory responses are essential for the removal of unwanted material from the breakdown of diseased or dying brain cells. Activated glial cells are the critical components of this response and assume greater importance with increasing age. When stimulated, reactive glia release free radicals to destroy foreign material and are part of the brain's immune protection.

With ageing, these processes may persist for longer than is required to maintain the health of the vasculature or neurones. Unchecked, apoptosis, inflammation and free radical generation can compromise membrane function and cause widespread, progressive neurodegenerative change. These changes may be highly circumscribed, affecting isolated brain regions, or may be generalised to large neuronal systems. It is quite reasonable to speculate that age-related cognitive impairment reflects relatively brief episodes of imbalance that are returned to normality, whereas dementia represents a chronic, unremitting over-activity of one or more of these processes that has persisted for at least several years and caused neuronal death and profound loss of synaptic density.

This model of age-related harmful change is incomplete without inclusion of the role of disease of the cerebral vasculature. Pathological change in the vessel wall can disrupt the multiple brain systems that support memory and can do so along routes other than the obvious occlusion of brain blood supply or, less often, haemorrhage into neural tissue. These changes to the cerebral vasculature involve much the same pathological processes that determine neural health, namely apoptosis, inflammation and free radical damage. In those patients where the health of neurones is jeopardised by exposure to any one or more of these processes, the health of the cerebrovascular endothelium may well be similarly affected. This potentially complex issue is illustrated by the effects of homocysteine on nervous and vascular tissue.

Hyperhomocysteinaemia

Homocysteine is a naturally occurring amino acid that is convert-

ed to methionine by folate/vitamin B_{12}; deficiency of these vitamins causes hyperhomocysteinaemia. Subjects with plasma homocysteine concentrations above 13 µmol/L are at greater risk of developing dementia over follow-up than those with lower homocysteine concentrations. Several studies have shown that higher homocysteine is also associated with greater cognitive ageing, accounting for about 8–12% of the variance in cognitive measures in old age.[14,15] Pathological mechanisms to explain these associations include the known potential of homocysteine to damage biological membranes and DNA and (in transgenic animal models) its capacity to sensitise neurones to the harmful effects of amyloid.

Epidemiology

Lack of precise definitions has influenced studies on the incidence and prevalence of vascular dementia. The decision to include or exclude patients whose dementia is associated with both Alzheimer-type and vascular dementia features ('mixed Alzheimer/vascular dementia') has produced considerable variation in incidence and prevalence rates. There are several good summaries of epidemiological data.[16-18] Overall prevalence rates for dementia in populations from Western Europe and North America suggest that, amongst those aged 65 or more, about 41–111 subjects per 1,000 at risk will be demented. Estimates from Asia tend to be lower than those from North America and Europe. Within the dementia spectrum, prevalence of vascular dementia is estimated at between five and 31 cases per 1,000 at risk. Reports from Japan suggest that the highest rates may be in the Far East whilst France (much as in stroke epidemiology) has reported the lowest rates of vascular dementia in the developed world.[19] There is general agreement, however, that the prevalence of vascular dementia increases steeply with age (again much in step with stroke).

The relative proportions of Alzheimer to vascular dementia cases is a little uncertain, largely because of problems arising from 'mixed Alzheimer/vascular' dementia cases. In broad terms, the proportion of Alzheimer cases is greater in Western developed nations than in Asia whilst the proportion of vascular cases may be greater in the Far East than in Europe. There is some agreement that there is a slight excess of female over male Alzheimers' disease sufferers. Higher vascular dementia rates are believed to occur in men, although this is not consistently reported. There are too few incidence data to make firm statements about vascular dementia but it is generally believed that incident cases of vascular dementia arise less often than Alzheimer dementia in Europe.

Risk factors for vascular dementia

Hypertension is the single most potent risk factor for the development of vascular dementia. A history of hypertension is probably about twice as frequent in vascular dementia than in non-demented old people.[20] Studies from Japan and the US show that hypertension is present in about two thirds of vascular dementia sufferers. However, associations of this type must be interpreted with caution as the presence of hypertension tends to strengthen a clinician's conviction that vascular disease is the underlying cause of dementia. This type of selection bias runs through all clinical studies of risk factors for vascular dementia and has led to the exclusion of patients with vascular risk factors from studies of Alzheimer's disease.

Several good studies, however, suggest that hypertension is indeed a risk factor for vascular dementia. Skoog *et al*.[21] traced vascular risk factor data from mid-life in subjects then at risk of cognitive decline some 10–15 years later. Comparison between those who developed dementia and those who did not showed that the risk of dementia (both Alzheimer's disease and vascular dementia) was associated with hypertension. Forette *et al*.[22] showed data from the Syst-Eur trial which supported an important role for hypertension in dementia: treatment of isolated systolic hypertension reduced the overall incidence of dementia (both vascular dementia and Alzheimer's disease) by about 50%.

The problem of stroke-related dementia raises a number of related issues. Dementia follows stroke in about 30% of those who survive.[23] Here, the issue of temporal precedence implying causation is an important confounder. When dementia has followed stroke, it is supposed that the stroke has caused a vascular dementia. Prospective clinical studies with informative data are few: the Framingham studies have shown that incidence of stroke is associated with a decline in cognitive function from pre-stroke ability levels but it is as yet unclear whether this type of decline is sudden and essentially non-progressive (until the next stroke) or whether it represents the onset of a slowly progressive dementia of the Alzheimer type. Kokmen *et al*.[24] have suggested from the Rochester County cohort that the incidence of Alzheimer's disease is about 50% greater than expected in patients following stroke. This type of observation suggests that vascular pathophysiology may be important in the development of Alzheimer's disease or may pose a significant additional burden on cognitive function such that the threshold for dementia is crossed.

Risk factors for vascular disease in general have also been associated with vascular dementia. These include smoking, diabetes, impaired respiratory function, a history of heart disease (especially myocardial infarction) and atrial fibrillation.

Key messages

- Vascular dementia does not follow the typical onset or pattern of progression of Alzheimer's disease
- Magnetic resonance imaging is the most sensitive imaging method for white matter abnormalities and haemorrhage
- With age, apoptosis, inflammation and generation of free radicals damage both neurones and the cerebral vasculature
- Hypertension is the single most important risk factor for the development of vascular dementia

Genetic risk factors for vascular dementia are largely unknown. In keeping with the concept that the apolipoprotein E (APOE) gene is associated with frailty in the elderly, possession of the APOE ε4 allele is associated with increased risk of Alzheimer's disease and vascular dementia.[25] No consensus exists on the precise role of the APOE ε4 allele in vascular dementia: most studies yield contradictory results possibly attributable to the use of imprecise validated criteria for the diagnosis of vascular dementia. One rare form of vascular dementia is termed cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) and some forms of cerebral amyloid angiopathy.[26] Such cases are exceedingly rare.

Treatment/modification of risk factors

Many risk factors for vascular dementia and white matter abnormalities have been identified, including age, hypertension, reduced respiratory function, diabetes mellitus and the presence of cerebrovascular disease or cardiovascular disease elsewhere.[27-31] Specific risk factors for particular subtypes of vascular cognitive impairment require further characterisation. There is some evidence that treatment of such risk factors ameliorates cognitive decline, for example[32] the treatment of hypertension with ACE inhibitors or calcium channel blockers has a better effect on cognition than treatment with diuretics or beta blockers.

There is a need for research into whether strategies to prevent cerebrovascular disease and stroke are also effective in preventing vascular cognitive impairment. Similarly, research is needed to further assess risk factors known to be associated with vascular cognitive impairment and to assess whether their modification prevents or even reverses cognitive decline.

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