Vascular cognitive impairment

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Cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia and contributes to cognitive decline in the neurodegenerative dementias. The current narrow definitions of vascular dementia should be broadened to recognise the important part cerebrovascular disease plays in several cognitive disorders, including the hereditary vascular dementias, multi-infarct dementia, post-stroke dementia, subcortical ischaemic vascular disease and dementia, mild cognitive impairment, and degenerative dementias (including Alzheimer's disease, frontotemporal dementia, and dementia with Lewy bodies). Here we review the current state of scientific knowledge on the subject of vascular brain burden. Important non-cognitive features include depression, apathy, and psychosis. We propose use of the term vascular cognitive impairment, which is characterised by a specific cognitive profile involving preserved memory with impairments in attentional and executive functioning. Diagnostic criteria have been proposed for some subtypes of vascular cognitive impairment, and there is a pressing need to validate and further refine these. Clinical trials in vascular cognitive impairment are in their infancy but support the value of therapeutic interventions for symptomatic treatment.

Lancet Neurology 2003; **2:** 89–98

Dementia affects around 7% of the general population older than 65 years, and 30% of people older than 80.[1–5] Twice as many people are affected if those with cognitive impairment that falls short of diagnostic criteria for dementia are included.[6,7] Prevalence is expected to double over the next 30 years,[8] making disorders of cognition a priority for health-care and social-care services. If traditional diagnostic classifications for subtypes of dementia are used, more than half of cases are due to Alzheimer's disease (AD), followed by vascular dementia, which yields 25–30% cases. Stroke is the second leading cause of death worldwide and is a major determinant of adult disability.[9] It has many sequelae, including cognitive impairment; hospital-based studies show that up to a third of stroke patients have dementia within 3 months of stroke.[10]

Advances in neurobiology and the introduction of the first symptomatic treatments for AD[11] must be contrasted with poor progress in the area of vascular dementia.[12] Concepts of vascular dementia have historically been based on stroke and the multi-infarct model.[12] However, recognition is increasing that several vascular pathologies (eg, subcortical ischaemic small-vessel disease), as well as cortical infarcts, can lead to dementia.[13–18] Recognition is also growing of a close relation between vascular dementia and AD. For example, vascular factors such as hypertension,[19] diabetes,[20,21] smoking,[22] and hypercholesterolaemia[23,24] are now deemed risk factors for AD as well as vascular dementia. Furthermore, the effects of vascular and AD pathologies are additive,[25,26] and in most population samples these disorders appear together.[27] Collectively, these relations have renewed interest in the nature of the pathology, pathophysiology, clinical features, treatment, and outcome of patients with vascular dementia. In an effort to review and clarify current knowledge, concepts, and methods for further inquiry, the International Psychogeriatric Association convened a special meeting on vascular cognitive impairment attended by many international specialists (please see acknowledgments for list of participants). Also present were representatives from Alzheimer's Disease International, the World Federation of Neurology Dementia Study Group, the US Food and Drug Administration, and the European Commission for Medicinal and Pharmaceutical Compounds. As a product of this special international meeting, we have reviewed the current state of scientific knowledge in the subject of vascular brain burden and identified key issues requiring clarification and research to advance knowledge in this area.

Terminology

There is now agreement that cognitive impairments associated with cerebrovascular disease extend well beyond the traditional concept of multi-infarct dementia. Variations in defining the cognitive syndrome, vascular causes, and

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brain changes associated with cognitive decline have resulted in various proposed diagnostic criteria. Clinically important cognitive impairments associated with vascular disease frequently do not fulfil traditional criteria for dementia, since these criteria are based on the concept of AD and require the presence of prominent memory impairment, which is not necessarily a prime symptom in vascular dementia. Consequently, studies of the prevalence, clinical features, imaging changes, and outcomes of cerebrovascular brain disease have been inconsistent, which has limited progress.

In an effort to avoid scientifically constricting definitions, and to avoid artificial distinctions between different severities of cognitive impairment, we use the term vascular cognitive impairment to refer to all forms of mild to severe cognitive impairment associated with and presumed to be caused by cerebrovascular disease. This term, therefore, includes vascular cognitive impairment without dementia and vascular mild cognitive impairment—that is, mild cognitive impairments that have a presumed primary vascular basis—as well as vascular dementia. Vascular cognitive impairment covers individuals who have cognitive impairment related to stroke, multiple cortical infarcts, multiple subcortical infarcts, or both, silent infarcts, strategic infarcts, small-vessel disease with white-matter lesions, and lacunae. Vascular cognitive impairment also plays an important part in patients with AD pathology who have coexisting vascular lesions.

Classification of sporadic vascular cognitive impairment

Sporadic vascular cognitive impairment is a broad clinico-pathological range that includes various apparently different disorders. Several clinically identifiable subtypes exist, although these are still poorly specified. The uniting feature is that vascular pathology either causes or makes a substantial contribution to the cognitive impairment (panel).

Multi-infarct dementia

Multi-infarct dementia reflects the traditional view that multiple large cortical infarcts are required for dementia to develop (figure 1).[28] However, this type of vascular dementia is only one of several and is not the most common type in elderly people, who are more likely to have mixed AD and vascular dementia.[29]

Classification and causes of sporadic vascular cognitive impairment

- Post-stroke dementia
- Vascular dementia
  - Multi-infarct dementia (cortical vascular dementia)
  - Subcortical ischaemic vascular dementia
  - Strategic-infarct dementia
  - Hypoperfusion dementia
  - Haemorrhagic dementia
  - Dementia caused by specific arteriopathies
- Mixed AD and vascular dementia
- Vascular mild cognitive impairment

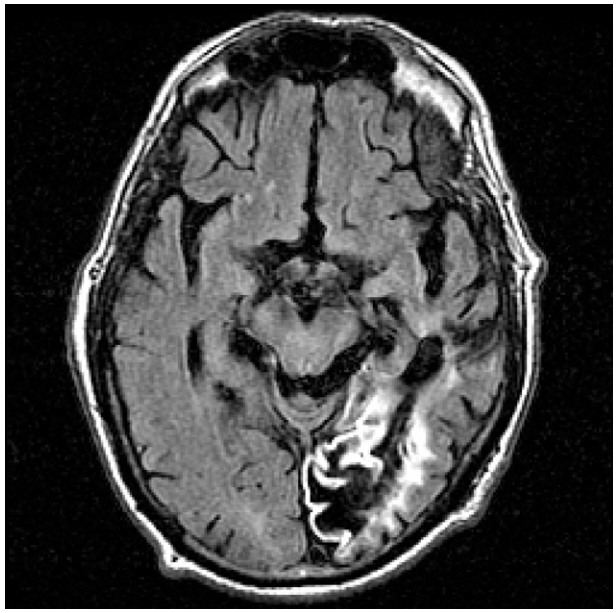

Figure 1. MRI scan (axial T1 sequence) showing large cortical infarcts in the dominant (left) hemisphere consistent with multi-infarct dementia.

Post-stroke dementia

Post-stroke dementia develops in up to a third of patients within a year of stroke[30] and is strongly associated with advancing age. Evidence suggests heterogeneity of the underlying pathology, with many cases resulting from different vascular causes and changes in the brain, as well as degenerative pathology. Post-stroke dementia includes cases with multiple corticosubcortical infarcts, strategic infarcts, subcortical ischaemic vascular dementia, and AD.

Subcortical ischaemic vascular dementia

A subtype of vascular dementia that has a generally predictable outcome is subcortical ischaemic vascular dementia, which incorporates small-vessel disease as the main vascular cause, with lacunar infarct and ischaemic white-matter lesions as the primary type of brain lesion (figure 2). The primary location of lesions is subcortical, and subcortical syndrome is the primary clinical manifestation.[29] Subcortical ischaemic vascular dementia incorporates the overlapping clinical entities of Binswanger's disease and the lacunar state.[31–33]

Clinical identification of patients with subcortical ischaemic vascular dementia can be based on a modification of criteria from the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) for probable vascular dementia.[34] These criteria require a relation between onset of dementia and cerebrovascular disease. In subcortical ischaemic vascular dementia, the onset is frequently more insidious, and temporal relations between the cognitive syndrome, brain-imaging features, and evidence of cerebrovascular disease may not be clear. Accordingly, the temporal-relation requirement was omitted from the research criteria for this disorder. The brain-imaging

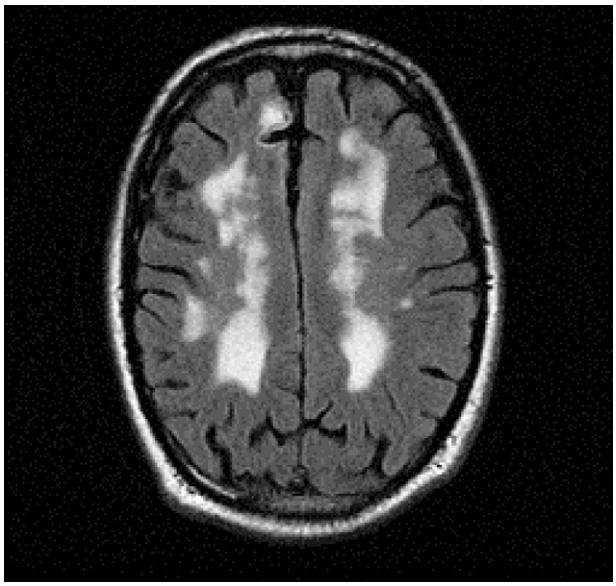

Figure 2. MRI scan (axial fluid-attenuated inversion recovery sequence) showing extensive white-matter lesions consistent with subcortical ischaemic vascular dementia.

criteria cover patients who have mainly white-matter lesions (the Binswanger type) and those with mainly lacunar infarcts (the lacunar state type).[34]

The classification of subcortical ischaemic vascular dementia may identify more homogenous and representative groups of patients and show more predictable clinical features, natural history, outcomes, and treatment responses than previous nosological constructs. Further research is needed to define the syndrome and stages of subcortical ischaemic vascular dementia, validate the brain-imaging criteria for the disorder by clinical-pathological correlation, and to characterise the natural history and outcomes of the syndrome. Identification of early and mild stages of subcortical ischaemic vascular dementia will also be an important area for research. Furthermore, specific markers, validated by clinical-pathological correlation, need to be identified to independently quantify vascular and AD burden.

Subcortical ischaemic vascular disease without dementia

Subcortical ischaemic vascular disease without dementia frequently manifests as white-matter lesions on MRI brain scans. These lesions can occur as early as 30 years of age, but their prevalence rises strikingly with age, and by 70 years of age at least 70% of the population is affected. Frequently, lesions occur in the context of well-recognised vascular risk factors. However, there also seem to be novel and poorly recognised risk factors for white-matter lesions, such as oxidative stress.[35,36] White-matter lesions have important cognitive consequences even in the absence of dementia.[37–39] Important non-cognitive consequences include depression and minor motor deficits (ie, gait disorder, imbalance, urinary frequency) that can impair quality of life.[40,41]

Mixed AD with cerebrovascular disease

AD with cerebrovascular disease (mixed dementia) has been underestimated as a common cause of dementia, particularly in elderly people.[29] Although common, this interaction is not recognised by current diagnostic systems, and, therefore, mixed dementia remains a difficult concept. Vascular and degenerative pathologies interact in terms of clinical expression of cognitive impairment,[27,30] and vascular dementia and AD share common pathogenetic mechanisms.[42] The nature of these inter-relations and the relative contribution of vascular and degenerative pathology to cognitive impairments in such mixed cases requires further study.

Vascular factors in AD

There is evidence of considerable cerebrovascular pathology in AD, including small-vessel disease and microinfarction, which suggests a substantial overlap between AD and vascular dementia. Vascular amyloid angiopathy is the most common vascular lesion reported in AD, present in virtually all AD cases, and apolipoprotein E ϵ4 is a strong factor in its development.[43] It can cause cognitive impairment independent of plaque and tangle pathology,[44] although its precise role in cognitive and non-cognitive features requires clarification. Vascular risk factors such as hypertension, arterial disease or atherosclerosis,[45] ischaemic heart disease, raised homocysteine,[46] smoking, and diabetes mellitus are also risk factors for AD, and markers of systemic vascular disease (eg, hypercholesterolaemia) are associated with the aetiopathogenesis of AD. These vascular pathologies may cause localised or global hypoperfusion (oligaemia), which may lead to AD pathology, white-matter lesions, or both. Genetic factors such as apolipoprotein E may modify the progression of AD in the presence of vascular disease. As such, the prevention or treatment of peripheral vascular disease may reduce risk of AD and mixed dementias.

Current diagnostic criteria for vascular dementia

Diagnostic criteria include those of the *Diagnostic and Statistical Manual*, fourth edition,[47] *International Classification of Diseases*, tenth edition,[48] ischaemic vascular dementia,[49] probable and possible vascular dementia,[50] and subcortical ischaemic vascular dementia.[34] Current criteria for vascular dementia are not interchangeable and the sensitivity and specificity of the proposed diagnostic criteria are variable.[51–54] None of the criteria sets distinguish mixed dementia (although they are better at excluding pure AD), nor recognise early disease, except those for subcortical ischaemic vascular dementia. For the most part, none of these criteria sets have been satisfactorily validated by prospective study and further progress must be driven by well-designed prospective clinical, radiological, and pathological studies. Structural brain imaging, especially MRI, remains the imaging method of choice for in vivo assessment of cerebrovascular disease, although functional brain imaging has potential in assisting with the differentiation of AD with associated brain infarction from vascular dementia.[55] Imaging criteria and early clinical manifestations will require careful review in the context of the existing criteria and there is a need for harmonisation of the criteria for subtypes of vascular dementia.

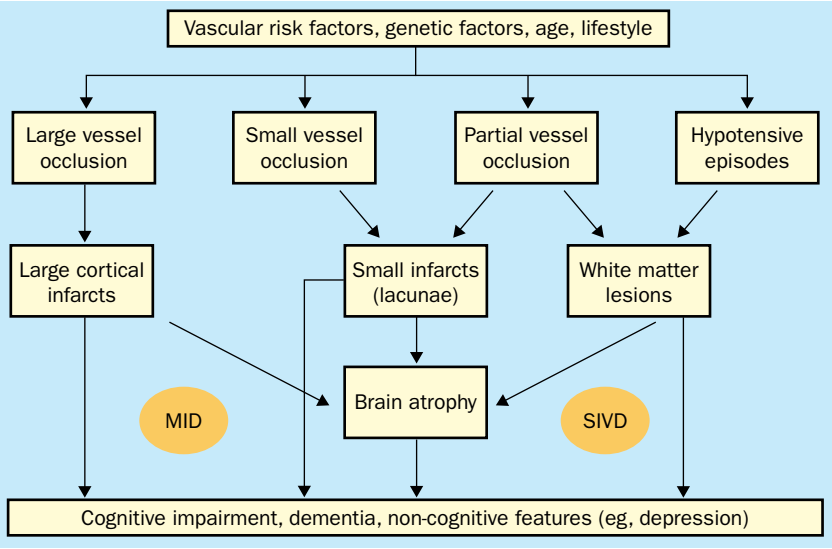

Figure 3. Summary of the main pathophysiological mechanisms in vascular cognitive impairment. MID=multi-infarct dementia; SIVD=subcortical ischaemic vascular disease.

Hereditary disorders associated with vascular cognitive impairment

The genetic contribution to stroke[56] and vascular dementia is important. The underlying genetic defects for several monogenic disorders have been identified.[57]

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a monogenic cause of ischaemic small-vessel disease and stroke in middle-aged individuals. Clinical manifestations include transient ischaemic attacks and strokes (80%), cognitive deficits (50%), migraine with aura (40%), psychiatric disorders (30%), and epilepsy (10%).[58] Mean age at onset is 46 years and MRI reveals a combination of small lacunar lesions and diffuse white-matter abnormalities.[59] The underlying vascular lesion is a unique non-amyloid angiopathy involving small arteries (100–400 μm) and capillaries primarily in the brain, but also in other organs. Diagnosis may, therefore, be established by skin biopsy. Ultrastructural examination reveals granular osmiophilic deposits within the vascular basal membrane, commonly in contact with degenerating smooth-muscle cells.

The disease is caused by mutations in the *NOTCH3* gene, which codes for a large transmembrane receptor. CADASIL mutations involve highly conserved cysteine residues in epidermal-growth-factor-like repeat domains. Expression of *NOTCH3* is restricted to vascular smooth-muscle cells. The mutations result in a selective accumulation of the extracellular domain of the receptor within blood vessels.[60]

The cerebral amyloid angiopathies encompass a heterogeneous group of disorders characterised by deposition of amyloid in the walls of leptomeningeal and cerebral cortical blood vessels. Clinical features include recurrent or multiple lobar haemorrhages, cognitive deterioration, and ischaemic strokes. MRI displays diffuse white-matter abnormalities and focal lesions that can be ischaemic or haemorrhagic. Vessels show amyloid deposition, cracking of single layers, microaneurysm formation, and fibrinoid necrosis. The rupture of such structurally weakened arteries results in cerebral haemorrhage, characteristically in the cortices (lobar haemorrhage), rather than the subcortical regions (basal ganglia, thalamus) typical in hypertensive haemorrhage. Several autosomal dominantly inherited forms of cerebral amyloid angiopathy can be differentiated by genetic, biochemical, and pathological findings.[57]

Pathophysiology of vascular cognitive impairment

Various vascular lesions may be associated with cognitive impairment.[61–64] The term vascular is not synonymous with ischaemic, and vascular may also be used in a broad sense related to vessel abnormalities. Some parenchymal lesions, such as diffuse white-matter changes or gliosis, can have non-vascular and vascular origins.

The consensus is growing that small-vessel diseases have a more important role in the field of vascular cognitive impairment than previously recognised.[34,65] Results of many pathological studies of demented patients have shown that multi-infarct dementia is rare, and the proportion of patients with subcortical ischaemic vascular disease is higher and, in most series, more important in terms of prevalence.[16,66] The primary vascular mechanism in subcortical ischaemic vascular disease is small-vessel disease.[64] Complete and incomplete infarction may be associated with these lesions (figure 3). Incomplete infarctions, which may manifest as white-matter lesions on MRI, are associated with more chronic, diffuse, and less severe ischaemia, resulting in selective loss of tissue elements in order of their vulnerability (neuron, oligodendrocyte, myelinated axon, astrocyte, endothelial cell).[67] Small-vessel disease is also associated with small infarcts (lacunae) and cortical brain atrophy.[67] The typical white-matter lesions in subcortical ischaemic vascular disease include extensive periventricular and deep lesions affecting especially the genu or anterior limb of the internal capsule, anterior corona radiate, and anterior centrum semiovale. The lacunae are located most frequently in the caudate, globus pallidus, thalamus, internal capsule, corona radiata, and frontal white matter. The ischaemic lesions in subcortical ischaemic vascular disease particularly affect the prefrontal subcortical circuits, which explains the major cognitive, behavioural, and clinical neurological features of this entity.[68]

A major issue that awaits clarification is the load or burden of vascular changes that is required to produce cognitive impairment. This is important in relation to vascular cognitive impairment and in determining the role of vascular lesions in other disorders such as AD and depression. Several approaches will be required to explore these features. Neuropathological study will better define the

type of small-vessel disease and the related tissue consequences, but may not be suitable for defining the threshold itself. Although lesion load is important, a simple threshold is unlikely to emerge since location is also important; a major challenge lies in developing methods that can integrate lesion volume and location in a meaningful way that can be correlated with cognitive impairment. Structural and functional neuroimaging (eg, MRI, perfusion and diffusion MR, and magnetisation transfer imaging) will have an important role in defining lesion extent and location.[69]

Cognitive and psychiatric symptoms

Because vascular cognitive impairment includes many diverse syndromes with varying causes, the striking differences in clinical presentation and course between its different forms are unsurprising. For example, single strategic infarcts will produce cognitive and other deficits that entirely depend on the location of the infarct. However, the characteristic neuropsychological profile of vascular cognitive impairment, particularly subcortical ischaemic vascular disease, is believed to frequently include early impairment of attention and executive function, with slowing of motor performance and information processing.[31,70] Episodic memory is believed to be relatively spared compared with that in AD.[32] Other cognitive functions are variably affected dependent on the pathological substrate in individual cases. Psychiatric symptoms are as common and important as in AD. Mood symptoms such as depression, emotional lability, and loss of volition (apathy) are particularly frequent and persistent in vascular dementia compared with those in AD.[33–36]

The absence of an agreed evidence-based definition or criteria for vascular mild cognitive impairment is a major obstacle to progress, with key implications for understanding the mechanisms of disease progression and secondary prevention. The concept of amnestic mild cognitive impairment is probably too limited in view of the early attentional, executive, and motor impairments in patients with early vascular pathology.[37,38] The psychiatric profile in vascular mild cognitive impairment has not been established, although there is a strong relation between cerebrovascular disease, particularly white-matter lesions, and depression,[39] which requires clarification across the spectrum of vascular cognitive impairment. Another factor is the possible importance of location of the ischaemic lesions (affecting the thalamocortical projections), which may predispose to the development of post-stroke depression.[71]

For vascular cognitive impairment in general, the neurobiological substrates of psychiatric and cognitive symptoms have yet to be clearly established. Evidence from other populations shows that, attentional impairments, slowed processing, executive dysfunction, and depression are probably associated with disruption to frontosubcortical circuits. Small-vessel disease leading to lacunae and white-matter lesions is likely to be particularly important. The relation between key symptoms and specific types and location of pathology remains to be established, although this information will be essential for the rational conceptualisation of these disorders and the development of targeted treatments. The variability of other symptoms probably relates to the site and extent of specific lesions.

Disease progression in vascular cognitive impairment

Perhaps surprisingly, in many studies progression rates in naturalistic studies of vascular dementia are similar to those in AD.[72] This finding contrasts with slower progression rates for patients with vascular dementia enrolled in randomised clinical trials, in which vascular risk factors are better controlled than in naturalistic studies.[73] Rates of 10–15% per year are generally accepted for progression of amnestic mild cognitive impairment, but very little is known about the natural history of vascular mild cognitive impairment in selected hospital cohorts or in population studies.[72,74,75] The lack of an accepted and reliable operational definition for vascular mild cognitive impairment will, however, make such studies difficult to undertake.

The contribution of white-matter lesions seen on MRI to clinical progression may be of great importance but remains to be established.[76] In particular, progression of lesions has not yet been clearly correlated with cognitive progression.[77] With current methods, more than 1 year of observation will be required to detect worsening of white-matter changes, and the selection of patients at high risk of lesion progression (eg, those with pre-existing moderate to severe white-matter changes or hypertension) may be required.[78] As yet, white-matter changes are not established as a surrogate marker for therapeutic studies designed to detect effects on disease progression. On a more overt level, in one study the development of cerebrovascular disease in long-term follow-up of an AD cohort was associated with a more rapid course of illness.[79]

Therapeutic implications

Primary prevention

The formulation of any primary preventive strategy depends on knowledge of pathophysiological mechanisms. Since brain vascular disease may be the result of various pathological disorders, strategies for prevention will vary accordingly. Brain vascular disease is only one manifestation of systemic processes affecting blood vessels throughout the body. The particular factors for a given individual that result in brain vascular disease rather than vascular disease in other organs are not well understood. In considering preventive strategies, primary processes (eg, vascular risk factors resulting in vascular disease) must be distinguished from secondary events (eg, vascular disease leading to stroke). Treatment of the primary factors is essential to prevent secondary changes and clinical disease. For example, it is better to prevent stroke by early and judicious treatment of arterial hypertension than by the detection and removal of established carotid atheroma. Early intervention may be important because vascular risk factors cause vascular injury very early in life, probably well before the fourth decade, but difficult since the early stages of vascular injury are clinically silent.

For primary preventive strategies to be successful, they must be based on the accurate identification of the specific processes by which vascular injury occurs. Further detailed

pathophysiological studies of how brain vascular pathology causes cognitive impairments are required, but current strategies should emphasise the early detection and adequate treatment of known vascular risk factors for vessel disease and stroke.

Secondary prevention

Major advances have been made in treatment of acute stroke, particularly in antiplatelet agents and thrombolytic treatments for ischaemic stroke,[80] although studies of putative neuroprotective agents have been disappointing.[81] Treatments for recurrent stroke prevention are now well established,[82] including antiplatelet agents, carotid endarterectomy, warfarin for atrial fibrillation, and blood-pressure lowering. Although data are still limited, trials of recurrent stroke prevention offer the opportunity to study stroke-associated cognitive decline and dementia.

Symptomatic treatment

Several large, well-conducted, randomised, double-blind, controlled trials have been done. Initial studies of several agents in vascular dementia, including vasodilators, nootropics, and antioxidants, were disappointing.[83] Other agents, such as propentofylline and memantine, have, to date, shown promising evidence of efficacy.[84,85] The calcium antagonist and vasodilator nimodipine has been studied and, although there is no overall evidence of efficacy in vascular AD,[86] beneficial effects may be seen in a subgroup of patients with subcortical vascular dementia[87,88] and further studies are continuing. Evidence suggests efficacy for cholinesterase inhibitors in vascular dementia. In a 24-week, double-blind, placebo-controlled trial of patients with possible and probable vascular dementia, according to the NINDS-AIREN criteria, 5 mg and 10 mg donepezil significantly improved cognition and global function by around 2 points on the widely used Alzheimer's Disease Assessment Scale-cognitive subscale, compared with placebo.[89,90] In a study of patients with vascular dementia or AD with cerebrovascular disease, 24 mg galantamine significantly improved cognition, compared with placebo, after 24 weeks (mean 2·7 points on the AD assessment scale); global functioning, activities of daily living, and behavioural symptoms also improved.[91] Results from further trials are awaited, but evidence thus far suggests cholinesterase inhibitors may prove beneficial in the treatment of vascular dementia, as they already have in the management of AD.

Trial design in vascular cognitive impairment

General issues

Trial designs and endpoints developed for studies of AD are not necessarily applicable to vascular cognitive impairment studies because of differences in cognitive profile, course, and rates of progression, and issues, such as variability and heterogeneity, of underlying pathology. The target in trials of vascular cognitive impairment should ideally be a homogenous group, such as patients with subcortical white-matter alterations and lacunae—ie, subcortical ischaemic vascular disease. For trials of this disorder, a primary endpoint of altered rate of decline, rather than a categorical endpoint such as conversion of vascular mild cognitive impairment to vascular dementia, may be preferable since it would allow assessment of vascular mild cognitive impairment and vascular dementia, which are different points on the vascular cognitive impairment range, by use of similar frameworks. These rate-of-progression endpoints would also be applicable to intervention trials in mixed dementia. The primary outcome variables should be multidimensional and include cognition, global function, activity of daily living functions, and behavioural symptoms. Assessment of executive function should be a prominent component of the cognitive assessment. Delayed recall of visual and verbal material with assessment of hippocampal volume could be used to investigate the likely contribution of concurrent AD pathology. Outcome measures specific to individual patients may be needed. Studies assessing disease progression will require longer duration (1–2 years) and serial assessments. Possible biomarkers of disease progression require further investigation. Ironically, the growing evidence that risk factors for cerebrovascular disease and stroke are also risk factors for AD will make these studies more difficult to interpret, but should help in the important task of sorting out what is due to vascular and what is due to AD pathology.

Brain imaging should be incorporated in the design for any trial of vascular cognitive impairment, with MRI as the essential method for phase III studies. Within each trial, standard methods of image acquisition and appropriate quality controls are required. To ensure good reliability between workers rating patients, homogenous assessment of eligibility, accurate assessment of baseline variables (eg, volume of white-matter lesions or lacunae), assessment of subsequent changes, and central reading of scans is required. Serial imaging is highly recommended to enable biological assessment of the effects of interventions. Currently, this approach shows the most promise as a putative biomarker for studies of disease progression. Rates of change of hippocampal volume in AD should be compared with those in vascular dementia to find out how specific hippocampal atrophy is for either disease.[92]

Specific issues for trials of symptomatic therapy

Given the variability in the clinical course of vascular cognitive impairment, the potential for symptoms to improve, and the non-linear deterioration, longer-term follow-up and an increase in sample size may be necessary compared with the situation in AD, in which decline is more predictable.

Performance-based cognitive assessment is essential as a primary outcome measure in trials of vascular cognitive impairment. Although the pattern of cognitive impairment overlaps in vascular cognitive impairment and AD, some differences are notable, especially in subcortical ischaemic vascular disease. Of particular note in this disorder is the prominence of frontal-lobe impairments (attention and executive function). Executive function is an umbrella term used to describe several different processes, including volition and planning, and can be assessed by tests of attention, psychomotor speed, mental flexibility, and verbal

Search strategy and selection criteria

Data for this review were identified from papers largely selected from the files and personal knowledge of the specialists who attended the meeting of the International Psychogeriatric Association. References were also obtained from Medline searches using the MeSH headings "Dementia, vascular", "Dementia", "Alzheimer disease", and "Cerebrovascular accident", and keywords "vascular", "vascular dementia" and "stroke". Other reports were identified from the reference lists from papers identified above. Articles for inclusion were selected by the authors as representing the most relevant and important work in the field and some additional references were subsequently incorporated at the request of reviewers.

fluency. The vascular equivalent of the Alzheimer's disease assessment scale–cognitive subscale[93,94] addresses these differences with additional tests—two-number cancellation tests, a maze test, delayed word recall, digit symbol substitution, and category retrieval for animals—that assess executive function. Analogous to the situation with AD, tests for vascular cognitive impairment will need to evolve and be refined in the light of new knowledge, especially about the natural history of the disorder.

There are special considerations for the assessment of activities of daily living based around the existence of comorbid disorders and disabilities from the vascular insults themselves (eg, paresis and sensory loss), which are relevant confounding variables. Executive function has a particular effect on function because of the need for separate measures of planning, sequencing, and doing the tasks. The disability assessment for dementia scale[95] combines these three approaches and seems well suited to assessment in vascular cognitive impairment. For vascular mild cognitive impairment, functional assessments sensitive to these symptoms have been developed that may prove useful.[96] Disease staging is appropriate in vascular cognitive impairment, as in AD, perhaps with the exception of major stroke and some types of cerebral haemorrhage. Staging (eg, by use of a system such as the Clinical Dementia Rating Scale or Global Deterioration Scale) has the advantages of assessing the whole range of dementia severities, encompassing multiple domains of disability, has few cultural and educational biases, and reflects real life changes that are meaningful to patients and their carers.[97] Existing instruments such as the BEHAVE-AD test[98] and the Neuropsychiatric Inventory[99] are appropriate to assess behavioural and psychological symptoms in dementia, and there seems no need to amend them for use in vascular dementia.

Carer interventions in AD have proven beneficial for patients and their caregivers—higher functioning in patients, delay in institutionalisation, reduction in prescribed medication, and less caregiver burden—and are applicable to vascular dementia.[100–104] The physical effects of stroke and the need for carers to provide practical care for patients with stroke can alter their attributional style and, therefore, their coping strategies.[105] Some behavioural symptoms, such as depression and emotional lability, may be particularly amenable to treatment,[106] although more studies are required. Economic features of vascular cognitive impairment have been rarely studied. The presence of comorbid disorders increases the costs of care, and the association between stage of dementia and costs is less than that in AD.[107]

Regulatory issues

Many issues are associated with drug development and in how clinical trials are done in vascular cognitive impairment because of the substantial heterogeneity in aetiopathogenesis. In addition to the difficulty of diagnosis, patients entering clinical trials vary greatly in many of the cognitive abilities tested as outcome measures. However, despite these difficulties, the development of new treatments must be encouraged.

Trials for vascular cognitive impairment should follow local, national, and international guidelines on ethics. Investigators should recognise and participate in processes to review and improve existing guidelines and should be sensitive to cultural differences in ethical values. Investigators should propose well-designed studies in earlier phases of the disease process, including prevention trials, and have early consultation with the various regulatory bodies such as the Food and Drug Administration or the European Commission for Medicinal and Pharmaceutical Compounds. Currently, regulatory bodies accept the use of NINDS-AIREN criteria for the diagnosis of vascular dementia in trials addressing symptomatic treatment. In the future, well-defined populations of patients with subcortical ischaemic vascular disease or AD with cerebrovascular disease should also be studied. In considering trials, vascular dementia is recognised as being heterogeneous, and may have a variable cognitive profile. The requirement that short-term memory impairment be present for a diagnosis of dementia must be changed. Dual primary outcomes (cognitive plus global or functional) with behavioural outcome scales are strongly recommended, and specific cognitive outcome measures appropriate for vascular dementia are required, where necessary.

Conclusions

To broaden the current narrow concepts of vascular dementia, we suggest that the whole range of cognitive impairments associated with cerebrovascular disease be recognised and studied under our proposed term vascular cognitive impairment to recognise this broad spectrum. Overall, the cognitive syndrome and brain-imaging criteria need to be refined and knowledge of the natural history, stages, and outcomes of vascular cognitive function expanded. Therefore, criteria for vascular cognitive impairment and homogeneous subtypes need to be developed through study into clinical features, course, genetics, imaging changes, and underlying pathophysiology. Appropriate subtypes would include subcortical ischaemic vascular disease and cortical multi-infarct dementia. Further research into vascular factors in mild cognitive impairment is especially necessary to properly identify subtypes, progression rates, and relation to amnestic mild cognitive impairment. This improved knowledge can be used to assist

the design of studies to investigate risk-factor interventions and disease-modifying treatments. Sample sizes will depend on the likelihood of change within the time frame of the study. Assessment of the cost-effectiveness of interventions will also depend on this kind of information. Improved trial design is dependent on knowledge of etiopathogenesis in addition to other criteria, such as the appearance of cerebrovascular disease on imaging or the cognitive state at diagnosis. Cause is consistently not specified in studies of vascular dementia and this serious omission must be corrected in future investigations. Specific markers of vascular dementia are also needed to validate clinico-pathological correlations for subcortical ischaemic vascular disease and for AD.

Currently, no standard treatment exists for vascular cognitive impairment, and little is known about primary and secondary prevention, apart from direct extrapolation from work in stroke. Future studies, directed to distinct causal and pathological factors (eg, the vascular and the AD burden of the brain), will be needed to enable therapeutic advances.

Acknowledgments

The authors would like to thank all the other participants in the International Psychogeriatric Association (IPA) meeting held in Madrid in November, 2001: Ove Almkvist, Karolinska Institute, Huddinge, Sweden; Frederik Barkhof, VU Medical Centre, Amsterdam, Netherlands; Rafael Blesa, Institut Clínic Malalties Sistema Nerviós, Hospital Clínic i Universitari, Barcelona, Spain; H Robert Brashear, Janssen Research Foundation, Titusville, NJ, USA; Karl Broich, Federal Institute for Drugs and Medical Devices, Bonn, Germany; Arne Brun, Lund University Hospital, Lund, Sweden; Christopher Chen, Singapore General Hospital, Singapore; Edmond Chiu, University of Melbourne, Kew, Victoria, Australia; Jenny Court, Newcastle General Hospital, Newcastle-upon-Tyne, England, UK; Martin Dichgans, Klinikum Grosshadern, Munich, German; Steven H Ferris, Aging & Dementia Research Center, New York, NY, USA; Mario Fioravanti, University of Rome, "La Sapienza", Rome, Italy; Gabriel Gold, University Hospitals of Geneva, Geneva, Switzerland; Paul Ince, Royal Hallamshire Hospital, Sheffield, England, UK; Domenico Inzitari, University of Florence, Florence, Italy; Raj Kalaria, Newcastle General Hospital, Newcastle upon Tyne, England, UK; Alexander Kurz, Technische University, Munich, Germany; Lenore Launer, National Institute on Aging, Bethesda, MD, USA; Hugh Markus, St George's Hospital, London, England, UK; Mary Mittelman New York University Medical School, New York, NY, USA; Etsuro Mori, Hyogo Institute for Aging Brain & Cognitive Disorders, Himeji, Japan; David Munoz, Hospital Doce de Octubre, Madrid, Spain; Zsuzsanna Nagy, OPTIMA, Radcliffe Infirmary, Oxford, England, UK; Armando Oliva, Federal Drug Administration, Rockville, MD, USA; Raymond Pratt, Eisai Inc, Teaneck, NJ, USA; ChengXuan Qiu, Karolinska Institute, Stockholm, Sweden; Philip Scheltens, Vrije Universiteit Medical Center, Amsterdam, Netherlands; Reinhold Schmidt, Karl-Franzens University, Graz, Austria; Ingmar Skoog, Sahlgrenska University Hospital, Goteborg, Sweden; Larry Sparks, Sun Health Research Institute, Sun City, AZ, USA; Albrecht Stoeffler, Merz & Co GmbH & Co, Frankfurt am Main, Germany; Shoona Vincent, Novartis Pharma AG, Surrey, England, UK; Anders Wallin, Institute of Clinical Neuroscience, Sahlgrenska University Hospital, Moelndal, Sweden; Peter J Whitehouse, Case Western Reserve University, Cleveland, OH, USA; Anders Wimo, Karolinska Institute, Huddinge, Sweden; RaijaYlikoski, University Hospital of Helsinki, Tuomo Hänninen, Finland.

Authors' contributions

All authors were involved in the selection of relevant scientific articles for this review and for the drafting of specific sections.

Conflict of interest

JTO has received travel sponsorship and honoraria from Janssen-Cilag, Pfizer, Novartis, Astra-Zeneca, Lundbeck, and Shire. TE has been a member of the speaker bureau for Astra-Zeneca, Boehringer-Ingelheim, Novartis, Merz, Pfizer, Janssen-Cilag, and an adviser for Aventis, Gedeon Richter, Janssen-Cilag, Lundbeck, Eisai, and Novartis, and has participated in clinical trials of nimodipine, propentophylline, and galantamine. BR has been a consult or received lecture fees or honoraria from Amersham, Aventis, Janssen-Cilag, Lilly, Lundbeck, Forest, Merz, Meda Corp, Health Care Resources Group, the Gerson Lahrman Group, the Dunn Group and JP Cowen, participated in clinical trials of memantine (Merz & Co Frankfurt), and holds stocks in Andrx Corporation. GR has acted as a consultant and is a member of speaker bureaus for Eisai, Pfizer, and Novartis. LP has received honoraria from Janssen-Cilag, Pfizer, and Bayer, and has participated in clinical trials of nimodipine and rivastigmine. PG is on speaker bureaus for Janssen, Dupont, Roche Laboratories, Boehringer Ingelheim, and Medical Economics, has consultant agreements with NPS, Eisai/Pfizer, Searle/Lorex, Roche Laboratories, Ketchum, AstraZeneca, GlaxoSmithKline, Warner-Lambert, Baxter, Rand, Solvay Pharmaceuticals, Consumer Healthcare Products Association, Janssen, Res Med, Pharmacia, Novartis, Cephalon, Boehringer Ingelheim, and Eli Lilly, is on the thought leader panel for the Weinberg Group, and Roche Laboratories and Bayer have provided medication for research studies. KR has received travel sponsorship from Janssen, Ortho, Pfizer, and Novartis, has consulted for Janssen-Cilag, Searle, HMR, Novartis, Bayer Canada, Pfizer Canada, Hoechst AG, and Parke Davis, and has participated in clinical trials of galantamine, propentofylline, and donepezil. AB has received consultancy fees from Pfizer, Eisai, Janssen-Cilag, Novartis, Lundbeck, Merz, and Abbott. SG has acted as a consultant for Eisai/Pfizer and Janssen-Cilag. SdeK has consulted or participated in research for Eisai, Pfizer, Janssen, Schwabe, and Novartis. JB, CB, CdeC, and TS have no conflicts of interest to declare.

Role of the funding source

This review was the result of an IPA meeting held in Madrid in November, 2001. The programme was organised and faculty invited by IPA. The meeting was funded with unrestricted educational grants from Eisai Inc and Pfizer Inc, Janssen-Cilag and Janssen Research Foundation, and Novartis Pharma AG. All programming decisions and the resulting review were developed by IPA with no sponsor involvement.

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