Subcortical ischaemic vascular dementia

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Vascular dementia is the second most common type of dementia. The subcortical ischaemic form (SIVD) frequently causes cognitive impairment and dementia in elderly people. SIVD results from small-vessel disease, which produces either arteriolar occlusion and lacunes or widespread incomplete infarction of white matter due to critical stenosis of medullary arterioles and hypoperfusion (Binswanger's disease). Symptoms include motor and cognitive dysexecutive slowing, forgetfulness, dysarthria, mood changes, urinary symptoms, and short-stepped gait. These manifestations probably result from ischaemic interruption of parallel circuits from the prefrontal cortex to the basal ganglia and corresponding thalamocortical connections. Brain imaging (computed tomography and magnetic resonance imaging) is essential for correct diagnosis. The main risk factors are advanced age, hypertension, diabetes, smoking, hyperhomocysteinaemia, hyperfibrinogenaemia, and other conditions that can cause brain hypoperfusion such as obstructive sleep apnoea, congestive heart failure, cardiac arrhythmias, and orthostatic hypotension. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) and some forms of cerebral amyloid angiopathy have a genetic basis. Treatment is symptomatic and prevention requires control of treatable risk factors.

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Panel 1. Clinicopathological classification of vascular dementia

Large-vessel vascular dementia
Multi-infarct dementia—multiple large complete infarcts, cortical or subcortical in location, usually with perifocal incomplete infarction involving the white matter
Strategic infarct dementia—a single infarct in functionally critical areas of the brain (angular gyrus, thalamus, basal forebrain, or territory of the posterior cerebral artery or anterior cerebral artery)

Small-vessel vascular dementia
SIVD
- Binswanger's disease
- Lacunar dementia or lacunar state (état lacunaire)
- Multiple lacunes with extensive perifocal incomplete infarctions
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)

Cortical-subcortical
- Hypertensive and arteriolosclerotic angiopathy
- Cerebral amyloid angiopathies (including familial British dementia)
- Other hereditary forms
- Collagen-vascular disease with dementia
- Venous occlusions

Ischaemic-hypoperfusive vascular dementia
Diffuse anoxic-ischaemic encephalopathy
Restricted injury due to selective vulnerability
Incomplete white-matter infarction
Border-zone infarction

Haemorrhagic vascular dementia
Traumatic subdural haematoma
Subarachnoid haemorrhage
Cerebral haemorrhage

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In order of prevalence, Alzheimer's disease, vascular dementia, and Lewy-body disease are the most common causes of dementia in elderly people.[1] Vascular dementia results from ischaemic, hypoperfusive, or haemorrhagic brain lesions that are manifest as numerous clinical syndromes (panel 1). Subcortical ischaemic vascular dementia (SIVD), due to small-artery disease and hypoperfusion, is clinically homogeneous and a major cause of vascular cognitive impairment and dementia. In this article, we review the progress made in the understanding of SIVD during the past decade.

Definitions and terminology

The term subcortical refers to lesions, and their manifestations, that predominantly involve the basal ganglia, cerebral white matter, and the brainstem (as opposed to cortical dementias). Dementia in SIVD is caused by ischaemic injury, which includes both complete infarction (lacunar infarcts and microinfarcts) and incomplete infarction of deep cerebral white matter. Lacunar infarcts or lacunes are small cavitated ischaemic infarcts of less than 15 mm in diameter. They are typically located in the basal ganglia, internal capsule, thalamus, pons, corona radiata, and centrum semiovale. White-matter lacunes can overlap with non-confluent areas of ischaemic white-matter changes. Microinfarcts are mostly non-cavitated and are found in cortical and subcortical structures. Their size can range from a few microns to about one-tenth of the size of lacunes.

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Pathological features of white-matter lesions in Binswanger's disease include: diffuse myelin pallor (that spares U fibres), astrocytic gliosis, widening of perivascular spaces (état crible), and lacunes in the basal ganglia and pons; loss of oligodendrocytes leading to rarefaction, spongiosis (vacuolisation), and loss of myelin and axons without definite necrosis (incomplete white-matter infarction), which finally culminates in white-matter necrosis and lacunes. The term Binswanger's disease is controversial and many other names have been proposed. However, we agree with Pryse-Phillips[3] that "the eponym presumes less and is preferred for its brevity". SIVD incorporates two old neuropathological and clinical conditions, the lacunar state (état lacunaire) and Binswanger's disease.

Pure incomplete white-matter infarction—similar to that observed in the penumbra of large infarcts—is typically seen in hypoperfusive disease.

Magnitude of the problem

In clinical studies, the proportion of vascular dementia caused by small-vessel disease ranges from 36% to 67%.[4] Lacunar infarcts are found in 10% to 31% of symptomatic strokes, with a population-based prevalence of 13·4 per 100 000 in white people,[5] although the prevalence is higher in oriental (Japanese and Korean), hispanic, and black populations and mixed ethnic groups.[4,6,7]

A significant proportion of subcortical lacunes are clinically silent.[8,9] In the population-based Cardiovascular Health Study, about a quarter of 3660 participants aged 65 or older had one or more lacunes on magnetic resonance imaging (MRI).[10] Most lacunes (89%) were clinically silent or were manifest as gait problems and subtle cognitive impairments that were not recognised as stroke. In other population-based studies the prevalence of silent lacunes ranged from 11% to 24%.[9,11–13]

Incomplete or non-cavitating ischaemic white-matter lesions of the brain—with or without lacunes—are common in elderly people. For example, only 4·4% of 3301 participants in the Cardiovascular Health Study did not have white-matter lesions; about 20% had extensive lesions and did worse on timed tests of manual dexterity, gait, and cognitive performance than individuals who had mild lesions.[14] According to several population-based studies, the prevalence of cerebral white-matter hyperintensities on MRI in elderly people is in the range of 62–95%.[15–18] These lesions are associated with advancing age, lacunes, hypertension, heart disease, orthostatic hypotension, smoking, and lower income and education.[14–19] Cognitive dysfunction and gait impairment are related to lesion severity.[19–21]

Pathophysiology of ischaemic brain injury

Figure 1 shows the two main pathophysiological pathways involved in SIVD. In the first, occlusion of the arteriolar lumen due to arteriolosclerosis leads to the formation of lacunes, which results in a lacunar state (état lacunaire). In the second, critical stenosis and hypoperfusion of multiple medullary arterioles causes widespread incomplete infarction of deep white matter[22] with a clinical picture of

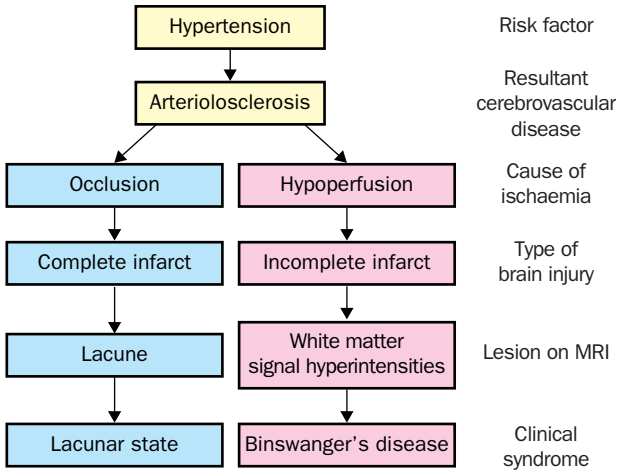

Figure 1. Two pathophysiological pathways of ischaemic brain injury. The pathway on the left is initiated by occlusion of an arterial lumen. This leads to discrete areas of complete infarction (ie, lacunar infarcts) and functional disruption within a distributed network (eg, dementia). The pathway on the right is defined by critical stenosis and hypoperfusion involving multiple small arterioles mainly in deep white matter. These two pathways often coexist in the same patient.

Binswanger's disease.[23] In practice, the two clinical pathways can overlap; lacunes and white-matter lesions are often seen together, which is not surprising given their common origins. In addition, a combination of small-vessel and large-vessel cerebrovascular disease in the same patient is not unusual. In over half of these cases, cortical and basal-ganglia microinfarctions may be present, even though these lesions are not apparent on MRI.[24]

Important physical principles and pathophysiological mechanisms involving the microcirculation in SIVD are summarised in panel 2. These mechanisms include haemorheological factors, increased resistance to flow, decreased autoregulation, endothelial changes, dysfunction of the blood–brain barrier, and dilatation of perivascular spaces. Their combined effects result in hypoperfusion and incomplete infarction of deep white matter.

Determinants of ischaemia

Ischaemia develops when tissue perfusion and the supply of essential nutrients such as oxygen and glucose become inadequate for the support of cell metabolism. The balance between supply and demand is influenced by differences in the oxygen and glucose requirements of different brain cells, regional differences in cerebral blood flow (CBF), and duration of hypoperfusion. Energy requirements are considered higher for neurons than for glia (neurons> oligodendrocytes>astrocytes>endothelial cells). However, experimental work has shown that oligodendrocyte swelling and vacuolar changes in myelin sheaths occur earlier and independently of neuronal injury.[25,26]

Incomplete infarction

Below a critical perfusion threshold, selective cell loss may occur without pronounced infarction or cystic necrosis. Selective neuronal loss occurs in the penumbra surrounding

Panel 2. Relevant haemorheological and autoregulatory circulatory factors in white-matter hypoperfusion

Haemorheological factors

Oxygen delivery to tissues depends on blood flow and red-cell concentration. The rate of blood flow through a tubular vessel is determined by Poiseuille's law.

$$\text{Blood flow} = \text{perfusion pressure} \times \pi \times \text{radius}^4/8 \times \eta \times \text{length}$$

Blood flow declines as the length of the vessel increases and its radius decreases. A salient feature of the equation is the overriding influence of vessel radius ($\pi \times \text{radius}^4$).

In vessels with a small, fixed radius (eg, in small-artery disease) the flow of blood is determined mainly by systolic blood pressure and by blood viscosity (η); ie, by the force (sheer stress) required to overcome the resistance of the tube wall to the fluid at a given flow velocity.

Blood is a non-homogeneous and non-newtonian fluid; ie, viscosity increases at slow velocities in the arteriolar bed and microcirculation. In vessels affected by arteriolosclerosis, the resulting hyperviscosity may slow down or halt blood flow.

In arterioles, there is disproportionate increase of blood viscosity with increases in haemoglobin concentration, plasma viscosity, red-cell deformability, hyperglycaemia and hyperlipidaemia.

Autoregulatory changes

Owing to anatomical features, local cerebral blood flow is lowest in periventricular and deep white-matter regions perfused by long, narrow, non-collateral end-arterioles.

Perfusion threshold for ischaemic injury increases if hypoperfusion persists over longer periods of time.

With autoregulation, when cerebral perfusion pressure falls, blood vessels dilate, increasing blood volume and initially maintaining regional cerebral blood flow (rCBF).

When blood flow starts to decline, oxygen extraction fraction (OEF) increases to maintain cerebral oxygen metabolism ($rCMRO_2$).

$$rCMRO_2 = OEF \times \text{arterial oxygen content} \times rCBF$$

When perfusion fails, pressure exceeds compensatory mechanisms and oxygen metabolism is compromised. Neuronal and glial function is lost followed by irreversible necrosis. In infarcted tissue, both $CMRO_2$ and OEF values are minimal. Thus, increased OEF is a transitional feature signalling a critical period of incipient ischaemia.

acute infarcts,[25] whereas selective loss of oligodendrocytes, myelin, and axons occurs in deep white matter of patients with severe stenosis of medullary arterioles.[27,28] This selective loss of tissue elements due to ischaemia is known as incomplete infarction[22,25,29] and may occur when systemic blood pressure drops below autoregulatory reserve, intracranial pressure exceeds mean arterial pressure, or there is severe stenosis of several arteries or arterioles.[27–29]

Data from experiments in animals suggest that the threshold for ischaemia is not fixed but depends on the duration of hypoperfusion. Reduction of CBF to 30–60% for 1–3 months in rats[30,31] and gerbils[32,33] produces impairments in memory and behaviour and patchy loss of neurons in the hippocampus, striatum, and cerebral cortex. Within 3 weeks, changes in the monoaminergic system can be detected,[34] and by 2 months, demyelination and gliosis are also observed.[35]

Haemorheological factors

As summarised in panel 2, oxygen delivery to tissues depends on blood flow and the concentration of red blood cells. A high concentration of red blood cells and raised plasma viscosity are important in the pathogenesis of Binswanger's disease.[36] Other clinically relevant haemorheological factors in SIVD include hyperglycaemia, hyperfibrinogenaemia, polycytaemia, hyperlipidaemia, and hyperviscosity.[36,37]

Decreased autoregulatory reserve in SIVD

Under normal conditions, autoregulatory mechanisms compensate for variations in mean arterial pressure of 60–150 mm Hg. In patients with chronic hypertension, the curve is shifted upwards—ie, these individuals are unable to compensate for rapid decreases in blood pressure.[38,39] In patients with Binswanger's disease, the range is narrowed and vasodilator capacity is impaired in response to carbon dioxide or acetazolamide.[40,41] Patients with small-artery disease and compromised autoregulatory reserve can be at increased risk of ischaemia if their blood pressure is abruptly lowered by postural changes (orthostatic hypotension), by overly aggressive antihypertensive treatment, or by cardiac failure with low systolic blood pressure (congestive heart failure and arrhythmias).

Decreased CBF in SIVD results, at least partly, from compromised vascular reserve. By use of positron emission tomography (PET) with oxygen-15-labelled water, Kuwabara and co-workers[41] found similar 25% decreases in resting CBF in patients with Alzheimer's and Binswanger's diseases. However, only those patients with vascular disease had an impaired vasoreactive response to hypercapnia (CBF increased by 1·8% in Binswanger's disease *vs* 5·7% in Alzheimer's disease). Impaired vasoreactivity in response to acetazolamide is found only in SIVD and not in multi-infarct dementia.[40]

Increased oxygen extraction fraction (OEF) in SIVD

Increased OEF is a marker of ongoing ischaemia and pending infarction. By use of ^{15}O-PET, Yao and colleagues[42] found that patients with Binswanger's dementia had reduced CBF and cerebral metabolic rate for oxygen ($CMRO_2$; 20–30% lower than normal in grey matter and 30–40% lower in white matter). Non-demented patients with Binswanger's disease had no significant changes in CBF and $CMRO_2$ in grey matter; however, a 30% reduction in CBF and a 130% increase in OEF were found in white matter. In a more recent ^{15}O-PET study,[43] CBF to the cerebral cortex and deep grey nuclei was decreased in patients with silent lacunes. These studies suggest the presence of occult misery perfusion in patients with SIVD.

Relationship between ischaemia and dementia

Severity of dementia in SIVD correlates more strongly with the degree of hippocampal and cerebral atrophy than with severity of white-matter hyperintensities.[44–46] Nonetheless, cerebral atrophy and white-matter lesions are related. Quantitative MRI reveals widespread atrophy in SIVD that is not solely due to focal infarction. Possible causes include concomitant Alzheimer's disease, deafferentation or metabolic idling, and hypoperfusion.

Neuropathology

Microangiopathy

SIVD has been called small-vessel dementia because changes in cerebral microcirculation have a central role in its pathogenesis.[29] Microangiopathy is mainly related to ageing,[47] arterial hypertension,[29] and diabetes mellitus[48] but other conditions, such as hyperhomocysteinaemia,[49] may also be important.

Changes of cerebral blood vessels with ageing

The occurrence of lacunes and white-matter changes increases exponentially after 65 years of age, which indicates the importance of morphological changes of cerebral microvasculature that occur with ageing.[47,50] In addition to lengthening and tortuosity (figure 2), the lumen of medullary arterioles in elderly individuals is progressively reduced due to arteriolosclerosis (figure 2). Concentric lamellar collagen fibres and deposition of fibrohyaline substance in the subadventitia, with negligible changes in media and intima, are seen on light microscopy.[47,50,53] Electron microscopy[51,54] shows proliferation of collagen fibres and accumulation of cellular debris and amorphous material in the subadventitia; amyloid is not present and angionecrosis is seldom seen.

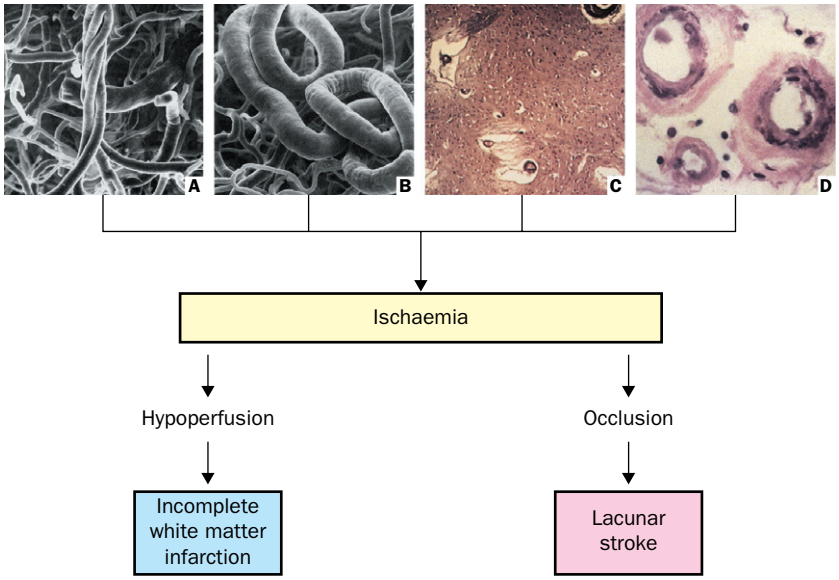

Figure 2. Factors leading to brain ischaemia and hypoperfusion in elderly people. Striking age-dependent morphological changes in brain vessels include tortuosity with formation of skeins in cortical arterioles (A) and elongation, which results in loops and tangles (B), particularly of long penetrating arterioles supplying deep white matter. Increase in blood-vessel length raises the blood-pressure threshold for perfusion of periventricular white matter at the distal end of these vessels. Furthermore, the lumen is stenosed by senile concentric arteriolosclerosis (D) often with calcification of vessels (C, top right). Under normal conditions, autoregulatory mechanisms induce vasodilation in response to decreases in mean arterial perfusion pressure; these mechanisms become inoperative in patients with arteriolosclerosis and calcified vessels (C). The elderly brain is therefore more susceptible to hypotension and pump failure (cardiac arrhythmias and congestive heart failure). Delivery of oxygen to tissues, and other metabolic exchanges, are impeded by increased thickness of vessel walls (D) and widespread état criblé (C) with enlargement of perivascular spaces of Virchow-Robin, which results from tortuosity of elongated arterioles. A, B, C, and D are reprinted with permission from Elsevier Science.[51,52]

The cause of this senile arteriolosclerosis remains unknown. It begins late in the fourth decade of life, increases in severity with age, is more prominent in the frontal lobe, and is followed by arteriolosclerosis in the parietal, occipital, and temporal lobes.[47] The severity of white-matter lesions in patients with Binswanger's disease increases in direct proportion to the degree of stenosis due to arteriolosclerosis of medullary arterioles.[55–57]

Hypertensive arteriopathy

The microangiopathy of arterial hypertension has been well studied.[8,58] The main lesions are microatheromata, lipohyalinosis, and fibrinoid necrosis. Minute foci of microatheromatosis (100–400 μm) produce stenosis or occlusion of arterioles in hypertensive individuals. Lipohyalinosis is a progressive disorganisation of small-artery walls, most commonly present in vessels of less than 200 μm in diameter, with subintimal deposits of a hyaline fibrinoid substance. Lipohyalinosis leads either to thrombotic occlusion of the lumen and lacunar stroke or to mural destruction with formation of microaneurysms and hypertensive cerebral haemorrhage. Fibrinoid angionecrosis occurs with extreme hypertension producing segmental narrowing, dilatation, and necrosis of the vessel wall with deposits of a brightly eosinophilic substance. The perivascular tissues and neuropil around the constricted spastic segments are destroyed and astrocytic oedema is present.[59]

White-matter lesions

Vascular lesions of the cerebral white matter are best visualised in whole-brain, myelin-stained sections that typically show myelin pallor sparing U fibres, astrogliosis, rarefaction of the neuropil, spongiosis,[60] état criblé, and loss of oligodendrocytes, myelin, and axons without definite necrosis.[61,62] In these areas, arteriolosclerosis of medullary vessels is invariably found, with thickened vessel walls, narrow lumens, and late calcification. Extensive white-matter lesions can also occur in cerebral amyloid angiopathy.[63] These patients carry an increased risk of warfarin-related intracerebral haemorrhage after ischaemic stroke (odds ratio=12·9).[64]

Collagenous thickening and occlusion of deep periventricular-draining veins has been postulated to be another factor in the production of deep hemispheric white-matter lesions.[65] Subependymal lesions[66] in the immediate vicinity of the ventricles correspond to decreased myelin, loss ependymal cells, reactive gliosis, and increased extracellular fluid. Subependymal lesions can be found at any age and are probably non-pathological.

Lacunes

Lacunes result from occlusion of lenticulostriate, thalamoperforating, and long medullary arterioles and must be distinguished from dilated perivascular spaces (état criblé).[67] Microscopically, état criblé cavities have a small vessel within the lacune (figure 2) and show no evidence of necrosis, macrophages, or tissue debris. On rare occasions single or widespread dilatations of Virchow-Robin spaces present with subcortical cognitive deficits.[68,69]

SIVD is commonly associated with cortical hypometabolism and hypoperfusion,[70] which result in cortical and hippocampal atrophy. A neuropathological study of 20 patients with ischaemic vascular dementia showed lacunar strokes and microinfarctions (11/20; 55%) and ischaemic hippocampal injury.[24] Arteriolosclerosis, severe large-vessel atherosclerosis, and microemboli causing cortical microinfarctions were also observed.

Neurochemical changes

Damage to the blood–brain barrier and chronic leakage of fluid and macromolecules, particularly in hypertensive patients, could contribute to white-matter injury. Increased concentrations of CSF proteins were found in individuals with white-matter lesions detected by brain imaging[70–72] and in brains from patients with Binswanger's disease at autopsy.[73,74] Increased concentrations of proteases, complement, immunoglobulins, and inflammatory cytokines may also contribute to glial and axonal damage.[75–77]

Genetic factors

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is the most common genetic form of vascular dementia. This autosomal dominant disorder of small cerebral vessels maps to chromosome 19q12[78] and is caused by mutations in the *Notch3* gene.[79,80] The diagnosis can be established by skin biopsy[81] with confirmation by immunostaining with a *Notch3* monoclonal antibody.[82] Widespread loss of smooth-muscle cells results in decreased regional cerebral blood volume; these values correlate inversely with cognitive performance.[83]

Autosomal dominant forms of cerebral amyloid angiopathy are characterised by deposition of amyloid in the walls of leptomeningeal and cerebral cortical blood vessels and are manifest clinically as recurrent lobar haemorrhages, cognitive deterioration, and ischaemic strokes.[84] Dementia in cerebral amyloid angiopathy of Dutch type correlates with severity of β-amyloid deposits in stenotic vessels but not with the number of plaques and tangles.[85] In familial British dementia with amyloid angiopathy,[86] Binswanger-type deep white-matter hyperintensities and lacunar infarcts are seen on MRI in the absence of intracerebral haemorrhages.

Other potential genetic factors in SIVD include polymorphisms in the genes encoding angiotensin-converting enzyme,[87] paraoxonase,[88] 5,10-methylenetetrahydrofolate reductase,[89] and apolipoprotein-E.[90]

Clinical features

The clinical manifestations of SIVD include psychomotor slowness due to loss of control of executive cognitive functioning, forgetfulness, and changes in speech, affect, and mood.[91] Symptoms are caused by the interruption of prefrontal-subcortical circuits by ischaemic lesions.[92,93] These circuits are known to be involved in executive control of working memory, organisation, language, mood, regulation of attention, constructional skills, motivation, and socially responsive behaviours.[94–96]

A recent population-based study of executive dysfunction in elderly people[97] showed a prevalence of mild impairment in one in three (33·7%) individuals and moderate to severe deficits in one in six (16·4%) individuals over the age of 60. More severe executive dysfunction was associated with advanced age, lower education, and hispanic ethnicity.[97]

Detection of the clinical features and symptom pattern of SIVD can vary according to the medical setting. In stroke and neurology services, focal neurological signs that result from cerebrovascular events are most commonly recognised. However, psychiatrists may put emphasis on a broader range of cognitive, mood, and psychiatric symptoms, whereas general practitioners and gerontologists may be more concerned with the impact of behavioural manifestations on the patient's carer.

Unfortunately, the mini-mental state examination (MMSE)[98] and the Cambridge cognition examination (CAMCOG)[99]—widely used bedside tests for dementia screening—overlook executive dysfunction. Clinical experience with appropriate tests indicates that frontal-system involvement predominates in vascular dementia. For instance, Wallin and co-workers[100,101] used the STEP analysis to show the presence of frontal or prefrontal-subcortical symptoms in 91% of patients with this dementia.

Frontal executive control

Frontal executive cognitive functions control volition, planning, programming, anticipation, inhibition of inappropriate behaviours, and monitoring of complex goal-directed, purposeful activities (eg, cooking, dressing, shopping, and housework).[91,93,95–97,102] Loss of executive function is a major component of cognitive disability and dementia, due to the loss of planning capacity, working memory, attention, concentration, stimuli discrimination, abstraction, conceptual flexibility, and self-control. Some patients are unable to initiate the required behaviour, whereas others fail to inhibit irrelevant behaviours. Most patients can perform the individual steps of a complex problem but are unable to come up with a correct solution.

Prefrontal-subcortical loops can be interrupted by lacunes in the striatum, globus pallidus, or thalamus or by white-matter lesions that disconnect the prefrontal or anterior cingulate cortices from their basal-ganglia or thalamocortical connections.[95,96] Interruption of the dorsolateral prefrontal-subcortical loop results in executive dysfunction; orbitofrontal-subcortical circuit lesions preclude frontal inhibition of the limbic system and are manifested by uninhibited behaviours, impulsivity, and

personality change.[96] The anterior cingulate (medial frontal) cortex mediates motivation, thus lesions of this circuit commonly result in apathy, abulia, and even akinetic mutism.[102]

Clinical manifestations

The clinical manifestations of SIVD can be separated into two groups. In the first, symptomatic lacunes present with acute sensory-motor deficits (pure motor hemiplegia, pseudobulbar palsy, and other lacunar syndromes). In the second, subacute manifestations include cognitive impairment, personality and mood disorders, gait disturbances, motor dysfunction, and urinary symptoms.[23,36] In clinical practice, however, most patients with SIVD present with a gradual course punctuated by acute deficits leaving residual subtle focal signs (arm drift, central facial weakness, and reflex asymmetry) as well as parkinsonian signs, small-step gait, unsteadiness, or unilateral incoordination.

The clinical picture of acute single-strategic lacunar dementia is characterised by the abrupt onset of cognitive impairment. This impairment is in many cases associated with confusion, apathy, psychomotor retardation, inattention, abulia, and other features of frontal-lobe dysfunction but with mild focal findings (eg, hemiparesis, central facial weakness, or dysarthria). This clinical picture is in most cases the result of lacunar strokes involving the inferior genu of the internal capsule,[103,104] thalamus,[105] or caudate nucleus.[106] Underlying white-matter changes and silent lacunes may also be present. Extensive frontal hypometabolism with decreased CBF has been documented in these patients as a result of diaschisis.[107]

Cognitive impairment in SIVD with pronounced executive dysfunction may be clinically "silent" to the physician. However, relatives and carers may report abnormal behaviour resulting from lack of strategic planning and reduced speed of cognitive processing. Memory disturbances are less severe than in Alzheimer's disease, and mainly include forgetfulness and problems with spontaneous recall that improve with cues and prompting. Language, calculation ability, and other higher cortical functions are preserved. Intact recognition and verbal fluency separate SIVD from Alzheimer's disease.[108]

A severe dementia syndrome is uncommon in SIVD. Recently, Kramer and colleagues[109] used formal measures of executive function to demonstrate executive dysfunction in non-demented patients with subcortical lacunes. Executive dysfunction was related to the extent of white-matter abnormalities but not to the number of lacunes.

Personality and mood disorders include apathy, irritability, and so-called vascular depression.[110] Dysarthria and pseudobulbar palsy may be also be present. Patients commonly complain of urinary symptoms such as nocturia and urge incontinence.

Gait disturbance in SIVD has been traditionally classed as "marche à petits pas"—a short-stepped, wide-based, apraxic gait with a tendency to fall.[111] Patients typically turn slowly on one leg (the compass sign). Slowing of motor function—as well as dysarthria, dysphagia, and mild focal motor deficits—are commonly found and seizures may occur. In some patients there is a striking preponderance of extrapyramidal features, such as hypomimia, hypokinesia, axial and limb rigidity, loss of postural reflexes, and frequent falls, generally without tremor.[112]

As the disease progresses, patients with SIVD limit their field of interest, show emotional instability, attentional loss, decreased ability to make associations, and difficulties in shifting from one idea to another, resulting in perseveration. At this stage, initiation of gait is still preserved and speed of locomotion is quite good, but in many cases magnetic gait and freezing may occur. As the disease progresses, postural instability can compromise gait initiation, equilibrium, turning, and mobility.

Assessment of patients

Populations at risk

Clinicians should suspect SIVD in patients who have behavioural changes suggestive of executive dysfunction, particularly in elderly patients with a history of hypertension, diabetes, cigarette smoking, hyperfibrinogenaemia, or obstructive sleep apnoea.[113] The presence of congestive heart failure,[114,115] cardiac arrhythmias,[116] or orthostatic hypotension[117] is also important in elderly patients. Hypoperfusion due to congestive heart failure is increasingly recognised as a significant risk factor for cognitive decline in old people, as well as a source of cerebral embolism. Congestive heart failure is the leading cause of hospital admissions in more developed countries and a growing problem in less developed countries.[118] A large Italian study[114] recently showed cognitive impairment in 26% of patients discharged from hospitals after treatment for heart failure. In older patients with heart failure, cognitive impairment was correlated with the degree of left-ventricular dysfunction and with systolic blood pressures below 130 mm Hg.[115,119]

Other populations at risk of unrecognised SIVD include patients in cardiac rehabilitation services who have had a coronary-artery bypass graft[120–122] and those in convalescence units recovering from major surgery,[123] particularly hip-fracture repair.[124]

Neuropsychological assessment

In a recent systematic review of the neuropsychological features of vascular dementia, Looi and Sachdev[125] confirmed that, despite some similarities with Alzheimer's disease, patients with vascular dementia have superior function in verbal long-term memory but greater impairment of frontal executive function.

Few bedside tests are available for the assessment of executive dysfunction. We have found the following tests useful in clinical settings: the CLOX test (a brief measure of executive control based on a clock drawing task);[126] the trail-making test part B; the behavioural dyscontrol scale[97] (based on Luria's kinetic melody);[127] the EXIT-25[128] (a structured interview for clinical assessment of frontal symptoms); and STEP[101] (a method for the assessment of cognitive, psychiatric, and neurological frontal subcortical symptoms and signs). Ferris[129] proposed a modification of the Alzheimer's disease

Panel 3. Criteria for SIVD

The criteria for the clinical diagnosis include all of the following:

Cognitive syndrome

Dysexecutive syndrome—impairment in goal formulation, initiation, planning, organising, sequencing, executing, set-shifting and maintenance, abstracting

Memory deficit—impaired recall, relatively intact recognition, moderate forgetfulness, and benefit from cues; may be mild

Deterioration from a previous higher level of functioning, interference with complex (executive) occupational and social activities not due to physical effects of cerebrovascular disease alone

Cerebrovascular disease

Evidence of relevant cerebrovascular disease by brain imaging

Presence or history of neurological signs consistent with subcortical cerebrovascular disease (such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, dysarthria, gait disorder, and extrapyramidal signs)

Clinical features supporting the diagnosis of SIVD include the following:

Episodes of mild upper motor-neuron involvement such as drift, reflex asymmetry, and incoordination

Early presence of a gait disturbance (small-step gait or marche à petits-pas magnetic, apraxic-ataxic, or Parkinsonian gait)

History of unsteadiness and frequent, unprovoked falls

Early urinary frequency, urgency, and other urinary symptoms not explained by urological disease

Dysarthria, dysphagia, extrapyramidal signs (hypokinesia, rigidity)

Behavioural and psychological symptoms such as depression, personality change, emotional incontinence, and psychomotor retardation

Features that make the diagnosis of SIVD uncertain or unlikely include:

Early onset of memory deficit and progressive worsening of memory and other cognitive cortical functions, such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging

Absence of relevant cerebrovascular disease lesions on brain CT scan or MRI

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assessment scale cognitive portion (ADAS-cog) called the vascular dementia assessment scale cognitive portion (VAS-cog) to include tests that assess executive domains for use in trials of vascular dementia. Román and Royall[91] emphasised that gait, balance, micturition control, and manual dexterity should be assessed in patients with vascular dementia to determine their functional status. A depression scale should also be used routinely in patients with SIVD.

Imaging

Brain imaging is crucial as a confirmatory test for SIVD since silent lesions commonly occur. A diagnosis of vascular dementia can rarely be reached in the absence of vascular lesions (stroke, lacunes, and white-matter changes) as shown on brain imaging. However, the ischaemic nature of lesions in SIVD must be assumed because the images are non-specific and their cause could be non-vascular.

Lacunar infarcts and white-matter lesions can be detected by computed tomography (CT) and MRI of the brain, but the two methods differ in sensitivity and, possibly, in specificity.[130,131] White-matter lesions are seen as bilaterally symmetrical areas of hypodensity on CT and as hyperintensities in the periventricular or deep subcortical white matter on FLAIR or T2-weighted MRI. They can be distinguished from territorial infarcts by their lack of correspondence with a specific vascular territory, well-defined margins, lack of wedge shape, lack of cortical involvement, and association with enlargement of ipsilateral sulci or ventricles. The abnormalities detected by CT and MRI are not identical in terms of number, site, and extension.[132] There is good interobserver agreement on visual scales, but different scales attribute different significance to the same radiological picture.[133]

MRI has higher sensitivity than CT for the detection of white-matter lesions, but some of the changes detected on MRI are thought to represent normal radiological features without pathological significance.

Lacunar infarcts are seen as round or oval cavitated lesions with a diameter less than 15 mm. In radiological studies, a limit of 3–20 mm is generally used, although the size of a radiologically detected lacunar infarct is slightly larger than that found at autopsy. In the chronic stage, lacunar infarcts are hypodense on CT scans, hyperintense on FLAIR or T2-weighted MRI, and hyperintense relative to CSF on proton-density MRI. Most of the CSF-isointense lesions on proton-density MRI at the level of anterior commissural or inferior putamen are perivascular spaces or état criblé. Lesions smaller than 1×2 mm are more likely to be enlarged perivascular spaces than infarcts.

Alzheimer's disease and vascular dementia

The clinical differentiation of vascular dementia from Alzheimer's disease with cerebrovascular disease can be difficult.[134] Over 60% of older patients with Alzheimer's disease present with incomplete white-matter infarction[22] and patients with anterior-choroidal-artery stroke may meet criteria for Alzheimer's disease.[135] The ischaemic score may provide additional elements for the diagnosis of the multi-infarct form of vascular dementia.[136] Stepwise deterioration, fluctuating course, history of hypertension, history of stroke, and focal neurological symptoms occur more commonly in vascular dementia than in Alzheimer's disease.

Careful interview of relatives and carers for the identification of progressive memory loss that occurred before the ictus can enable a diagnosis of prestroke dementia in about 16% of patients with apparent poststroke dementia.[137]

Pre-existing mild cognitive impairment,[138] with isolated deficits in episodic and semantic memory, is another predisposing factor; both cognitive decline and incident Alzheimer's disease occur at a higher rate among patients with mild cognitive impairment than in cognitively intact age-matched controls.

Vascular risk factors may predispose not only to vascular dementia but also to the development of Alzheimer's disease.[139] These factors include hypertension, carotid-artery wall thickness, hypercholesterolaemia, peripheral vascular disease, apolipoprotein E ε4 allele, and hyperhomocysteinaemia. However, a major risk factor in older patients with mild Alzheimer's disease lesions is the presence of one or two basal-ganglia lacunes that increase the risk of clinical expression of the dementia more than 20 times.[140]

Recently, Du and co-workers[141] showed that patients with SIVD have smaller volumes of the entorhinal cortex and hippocampus than normal controls. However, despite

similar degrees of dementia severity, these MRI volumes were significantly smaller in Alzheimer's disease than in SIVD. When hippocampal and global atrophy measurements were included, substantial improvement in accuracy was achieved in the classification of normal controls and patients with Alzheimer's disease or SIVD.

Potential biomarkers

Wallin and Sjögren[142] studied the concentrations of two cytoskeletal proteins—tau and the light subunit of neurofilament protein (NFL)—in the CSF of patients with SIVD. NFL concentrations in CSF were raised, whereas tau concentrations were normal. The serum/CSF albumin ratio was increased, indicating vessel-wall damage and breakdown of the blood–brain barrier. By contrast, increased concentrations of tau in CSF are generally found in Alzheimer's disease. Combination of CSF biomarkers and CBF could aid differential diagnosis, but the sensitivity and specificity await confirmation.

Diagnostic criteria

Current criteria for vascular dementia are not interchangeable and their sensitivity and specificity are variable. Furthermore, none of them can distinguish mixed forms of dementia, such as Alzheimer's disease plus cerebrovascular disease, and prospective validation is missing. Panel 3 summarises the proposed clinical criteria for the diagnosis of patients with SIVD[143] based on a modification of the National Institute of Neurological Disorders and Stroke and the Assocation Internationale pour la Recherche et l'Enseignement en Neurociences (NINDS-AIREN) criteria for probable vascular dementia.[144] The main modifications include a clear delineation of the cognitive syndrome and of the relevant radiographic images consistent with cerebrovascular disease. Brain imaging requirements (panel 4) reflect the essential pathological changes of SIVD (construct validity) and their main variations (content validity), including white-matter lesions and lacunes. Accordingly, patients with corticosubcortical infarcts, haemorrhages, and specific causes of white-matter lesions are excluded by brain imaging.

Clinically, the importance of memory loss in the cognitive deficit has been decreased, whereas the relevance of the dysexecutive syndrome has been emphasised. The original NINDS-AIREN criteria for probable vascular dementia also require a temporal correlation between time of stroke onset and dementia. In SIVD, the onset is insidious in many cases and this temporal requirement has been omitted. Finally, both clinically supportive and uncommon features of SIVD are listed. The validity, sensitivity, and specificity of these criteria await validation.

Prognosis, prevention, and treatment

Older age, fewer years of education, lacunar strokes, larger white-matter lesions, and possibly race are all risk factors for the development of dementia after ischaemic stroke. In patients with lacunar stroke, the presence of extensive white-matter lesions is a poor prognostic sign and increases the risk of recurrent stroke (odds ratio=6·4), dementia (odds ratio=11·1), and death (odds ratio=4·6).[10] Prospective, community-based studies and short-term clinical trials indicate that control of risk factors for vascular disease—in particular hypertension[145] and hyperlipidaemia[146]—reduces the risk of cognitive impairment.

Panel 4. Brain imaging criteria for SIVD

CT

Extensive periventricular and deep white-matter lesions: patchy or diffuse symmetrical areas of low attenuation, of intermediate density between normal white matter and CSF, with ill-defined margins extending to the centrum semiovale, and at least one lacunar infarct

MRI

Binswanger-type white matter lesions: hyperintensities extending into periventricular and deep white matter; extending caps (>10 mm as measured parallel to ventricle) or irregular halo (>10 mm with broad, irregular margins and extending into deep white matter); and diffusely confluent hyperintensities (>25 mm, irregular shape) or extensive white-matter change (diffuse hyperintensity without focal lesions); and lacune(s) in the deep grey matter

OR

Lacunar cases: multiple lacunes (>5) in the deep grey matter and at least moderate white-matter lesions; extending caps, irregular halo, diffusely confluent hyperintensities, or extensive white-matter changes

AND

Absence of haemorrhages, cortical and/or corticosubcortical non-lacunar territorial infarcts and watershed infarcts; signs of normal pressure hydrocephalus; and specific causes of white-matter lesions (eg, multiple sclerosis, sarcoidosis, and brain irradiation)

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Drug treatments for vascular dementia

Potential targets for the treatment include improvement of core symptoms (cognition, executive function, and behaviour), psychiatric manifestations (mood changes), and slowing of disease progression. Few drugs have been tested in controlled clinical trials of vascular dementia, and only a handful of these trials recruited patients with SIVD.[147] The purported efficacy of vasodilators, such as nicotinic acid, cyclandelate, and papaverine, is based on uncontrolled open-label trials. Agents with modest efficacy in vascular dementia, as shown in randomised, controlled trials (class I evidence), include piracetam, oxiracetam, nicergoline, citicoline, pentoxifylline, propentofylline, aspirin, triflusal, and *Ginkgo biloba*.

A trial of the calcium-channel antagonist nimodipine was the first to address SIVD specifically,[148] which led to the current larger multicenter European trial. Memantine, a moderate-affinity non-competitive antagonist of the *N*-methyl-D-aspartate receptor, appears to counteract glutamate-induced excitotoxicity after ischaemia. A recent placebo-controlled trial of memantine (20 mg/day) in patients with mild to moderate vascular dementia (n=321) showed improved cognition, stabilisation of global functioning and behaviour, and good tolerance and safety.[149]

Search strategy and selection criteria
Articles were identified by searches of Medline, Current Contents, and from relevant books and the authors' extensive files. The search terms "vascular dementia", "subcortical dementia", "vascular cognitive impairment", "lacunar stroke", and "Binswanger's disease" were used. Recent articles were preferentially selected.

Cholinesterase inhibitors

Several studies have addressed the potential use of cholinergic agents, such as donepezil hydrochloride, rivastigmine tartrate, and galantamine hydrobromide for the treatment of vascular dementia. These agents have already been approved for the treatment of Alzheimer's disease. Rivastigmine and galantamine have been investigated in patients with mild to moderate Alzheimer's disease with stroke and vascular risk factors. In a small open-label trial (n=16) of rivastigmine,[150] stabilisation and mild improvement in the CLOX test was seen in patients with SIVD after a year. In a recent galantamine trial (n=592), about 40% of patients had probable vascular dementia according to NINDS-AIREN criteria.[151] Cognitive function, as measured by the ADAS-cog test, was significantly improved compared with placebo. The clinician's interview-based impression of change plus caregiver input (CIBIC-plus), behavioural measures (neuropsychiatric inventory), and activities of daily living (disability assessment in dementia) improved or remained stable in the treated group. However, the study was not powered for subgroup analyses of the patients with pure vascular dementia.

Donepezil was studied in two large trials (n=1219) of pure, probable, and possible vascular dementia[152] in which patients were recruited according to the NINDS-AIREN criteria. Patients were randomly assigned to either a low dose (5 mg/day), a high dose (10 mg/day), or placebo for 24 weeks. The patients selected clearly differed from cases of Alzheimer's disease plus cerebrovascular disease in that they showed less cognitive decline in the placebo group than the cases of Alzheimer's disease. The two treated groups showed significant improvement in cognitive scores (ADAS-cog, MMSE) and global scores (CIBIC-plus), compared with placebo. Donepezil was well tolerated by patients with a high frequency of cardiovascular and cerebrovascular pathology.

Other agents

Treatment of depression and anxiety in patients with SIVD may require antidepressants such as the serotonin-specific reuptake inhibitors sertraline and citalopram. The use of tricyclic antidepressants in elderly patients with vascular dementia is discouraged owing to their anticholinergic effects, including orthostatic hypotension. Atypical antipsychotic drugs, such as risperidone and olanzapine, can be useful in patients showing agitation and disruptive behaviours. However, cholinergic medications help to control these problems in many patients.

Conclusion

The subcortical form of vascular dementia is one of the commonest causes of cognitive decline in elderly people. SIVD is commonly not recognised and remains undiagnosed, but it accounts for a significant number of cases of dementia, recurrent falls in old age (and subsequent hip fractures), and incontinence and results in many admissions to nursing homes. It is therefore a heavy burden on public health; better recognition of the disease is necessary for maximum benefit to be derived from treatments that are currently available to delay disease progression, as well as the introduction of primary and secondary prevention measures.

Authors' contributions

GCR contributed the overall plan of the review, clinical and epidemiological aspects, pathophysiology (including figure 2), prevention and treatment, and the final version of the paper incorporating the revisions from all the coauthors. TE planned the review, contributed to the sections on radiological findings, clinical features, diagnostic criteria, treatment, and prevention. AW contributed to the sections on clinical findings, neuropsychological assessment, differential diagnosis, biomarkers, prevention, and treatment. LP contributed to the sections on definitions, neuropathology, pathophysiology, treatment, and prevention. HCC contributed the section on pathophysiology (including figure 1), and to the sections on neuropathology, epidemiology, assessment of patients, and prevention.

Conflict of interest

GCR is adviser and member of the speaker bureau for Eisai, Pfizer, and Janssen, and participated in the clinical trial of donepezil in vascular dementia. TE has been a member of the speaker bureau for Astra-Zeneca, Boehringer-Ingelheim, Novartis, Merz, Pfizer, and Janssen-Cilag, and an adviser for Aventis, Gedeon Richter, Janssen-Cilag, Lundbeck, and Novartis; he has participated in clinical trials of nimodipine and galantamine. AW is an adviser and a member of the speaker bureau for Eisai, Pfizer, Janssen, and Novartis-Sweden, and participated in the Nordic nimodipine trial. LP is an adviser for Eisai, Pfizer, Janssen, and Bayer and participated in clinical trials of nimodipine in vascular dementia. The above-named companies had no role in the preparation of this review or the decision to submit the paper for publication. HCC has no conflicts of interest to disclose.

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