Neuropsychiatry of cerebrovascular disease

CHAPTER 14

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Cerebrovascular disease is the second leading cause of death among non-communicable diseases worldwide[1]. There are key neuropsychiatric consequences which interfere with patients' daily function including cognitive impairment, mood disorders (depression), anxiety, and apathy[2]. While cerebrovascular disease is mostly managed by neurologists in an acute phase, psychiatrists also have important roles in diagnosing and managing these neuropsychiatric issues in the subacute to chronic phase of the condition. This chapter will provide an overview of cerebrovascular disease. Then, we will focus on the neuropsychiatric aspects of the disease, particularly vascular cognitive impairment and dementia, post-stroke depression, and post-stroke apathy.

1. Cerebrovascular disease

1.1 Definition

Cerebrovascular disease is classified into two types: *ischaemic stroke* and *haemorrhagic stroke*. **Ischaemic stroke** is the most common type and is caused by blood vessel occlusion that limits blood flow to the brain, resulting in brain tissue death (cerebral infarction**). Haemorrhagic stroke** is caused by rupture of a blood vessel which results in bleeding into the brain parenchyma (intracerebral haemorrhage: ICH) and subarachnoid space (subarachnoid haemorrhage: SAH).

Another important manifestation of ischaemic cerebrovascular disease is **transient ischaemic attack (TIA)**, which is a brief episode of neurological dysfunction resulting from focal cerebral ischemia that does not proceed to permanent cerebral infarction. Whereas TIA has been operationally described as symptom lasting less than 24 hours, symptoms typically last less than an hour[3]. Normally, TIA is defined by clinical syndrome with a fully reversible course, but advanced magnetic resonance imaging (MRI) can find small brain injuries in 30-50% of cases. Therefore, sometimes TIA is pragmatically paired with minor ischaemic stroke as part of a spectrum.

A more insidious manifestation of ischaemic cerebrovascular disease is **cerebral small vessel disease** which is defined as brain lesions caused by pathological process involving small vessels including arterioles, capillaries, and small venules supplying white matter and deep grey matter[4,5].

1.2 Epidemiology

Strokes affect 15 million people annually worldwide, with 85% being *ischaemic strokes* and 15-20% are *haemorrhagic strokes***.**

Stroke mortality is substantial, with the mortality rate in the United States being approximately 39.0/100,000 person-years in 2023[6]. Almost half of patients who survive more than 6 months after a stroke are dependent for at least one activity of daily living[7].

1.3 Pathophysiology

Ischaemic stroke is caused by impaired blood perfusion to the brain tissue. Most stroke incidence results from blood clots (occlusion) of cerebral blood vessels including the intracranial branches of the two internal carotid arteries anteriorly and the vertebrobasilar system posteriorly[8]. Only small groups of patients have stroke from secondary causes such as global hypoperfusion from systemic

hypotension or hypoxemia. All mechanisms will lead to hypoxia within brain cells, free radical generation and oxidative stress, inflammation, and eventually neuronal injury and death[9]. There are many recent classifications for the aetiologies of ischaemic stroke but the most famous is **the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification** that helps us categorize the different pathways by which ischaemic stroke occurs (Table 1)[10].

Haemorrhagic stroke, mainly intracerebral haemorrhage (ICH), is caused by rupture of blood vessels resulting in bleeding into brain parenchyma. Large hematomas will create direct pressure effects on nearby brain tissue causing neuronal injury, and ongoing hematoma will lead to increased intracranial pressure and extensive cerebral oedema. Locations and mechanisms of ICH can be differentiated into lobar ICH and deep ICH. Deep subcortical ICH is usually also caused by arteriolosclerosis which comes from thickening of the inner layer and dilation of small arterioles, mostly from chronic hypertension[11]. On the other hand, lobar ICH predominantly results from cerebral amyloid angiopathy, which is caused by abnormal amyloid aggregation within arterial walls[12]. As for non-traumatic subarachnoid haemorrhage (SAH), the most common cause is a spontaneous rupture of intracranial aneurysms (80-85%)[13].

Table 1: TOAST classification of stroke

Types	Explanation and examples of aetiologies
1. Large-artery atherosclerosis	Patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major artery or branch cortical artery, presumably due to atherosclerosis. This can be caused from direct thrombosis or artery-to-artery embolism.
2. Cardioembolism	2.1 High risk sources (high propensities for embolism): mechanical prosthetic valve, mitral stenosis with atrial fibrillation, atrial fibrillation (other than lone atrial fibrillation), left atrial/atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction (<4 weeks), left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, infective endocarditis 2.2 Medium risk sources: mitral valve prolapse, mitral annulus calcification, mitral stenosis without atrial fibrillation, left atrial turbulence (smoke), atrial septal aneurysm, patent foramen ovale, atrial flutter, lone atrial fibrillation, bioprosthetic cardiac valve, nonbacterial thrombotic endocarditis, congestive heart failure, hypokinetic left ventricular segment, myocardial infarction (>4 weeks, <6 months)
3. Small vessel disease	This often labelled as lacunar infarction. Typical mechanism includes arteriolosclerosis, lipohyalinosis, or fibrinoid necrosis, occur from chronic hypertension and diabetes.
4. Stroke of other determined aetiology	This category includes rare causes of stroke, such as non-atherosclerotic vasculopathies, hypercoagulable states, hematologic disorders, or hereditary vascular disorders.
5. Stroke of undetermined aetiology	In several instances, the cause of stroke cannot be determined with confidence which some patients will not have likely aetiology despite an extensive evaluation.

(Adapt from Adams HP et al 1992[10])

1.4 Presentation and course of illness

Ischaemic stroke usually presents as sudden neurological deficits, with the nature and extent of these deficits characterized by the location and size of the stroke lesion. Cerebral infarction from the internal carotid artery system (anterior circulation stroke) usually manifests as sudden unilateral motor and sensory deficits (hemiparesis and hemi-paraesthesia) and cortical signs. If infarction occurs in the dominant cerebral hemisphere (mostly on the left side), it often results in language impairment (aphasia) while right-sided stroke generally causes hemi-spatial neglect on the left side. On the other hand, vertebrobasilar artery stroke (posterior circulation stroke) fundamentally presents as sudden cranial nerve deficits and ataxia because of injuries to cranial nerve nuclei and the cerebellum, in addition to motor and sensory deficits from injury to the descending tracts. Symptoms usually include diplopia, dysarthria, dysphagia, dizziness, and gait ataxia. The disease course usually reaches maximum deficits right after onset and may be stabilized or improved overtime. However, symptoms can progress more dramatically in large vessel occlusion which could result in malignant cerebral oedema and eventually death in severe cases.

Haemorrhagic stroke tends to have more severe presentation and a higher mortality rate. Typical features include sudden neurological deficits similar to ischaemic stroke but often accompanied by headache, vomiting, and decreased level of consciousness because of increased intracranial pressure.

1.5 Investigation and management

All patients with sudden or acute-onset neurological deficits should be rapidly evaluated. Emergency brain imaging with computerized tomography (CT) or magnetic resonance imaging (MRI) should be done in all patients to exclude ICH. Vascular imaging, for example, CT or MR angiogram, also has important roles for patients with suspected large vessel occlusion (LVO) by helping select eligible patients for thrombolysis and endovascular treatment[7].

Ischaemic stroke treatment seeks to restore blood flow and function for patients. There are two main acute stroke reperfusion therapies including *Intravenous thrombolysis (IVT)* which injecting potent thrombolytic agents to cleave blood clots, and *Endovascular thrombectomy (EVT)* which using endovascular catheterization to extract blood clots from the vessel. Supportive and symptomatic treatments are necessary in subacute phase including admission to stroke unit care, secondary prevention of vascular risk factors, and rehabilitation by multidisciplinary teams[7].

Spontaneous ICH can be managed by both medical and surgical treatments. Lowering blood pressure and reversal of any anticoagulants are critical initial therapies to limit ongoing bleeding. Hematoma evacuation may be indicated in selected cases with large hematomas at risk of brain herniation[14]. **SAH from ruptured aneurysms** requires surgical intervention by clipping or endovascular treatment by coiling to obliterate the aneurysmal pouch[15].

2. Neuropsychiatric aspects of cerebrovascular disease

2.1 Vascular cognitive impairment and dementia

2.1.1 Definition

The American Heart Association and American Stroke Association (AHA/ASA) published a joint scientific statement in 2011, defining the term "Vascular Cognitive Impairment" (VCI) which encompasses all cognitive disorders associated with cerebrovascular disease[16]. The most recent Revised diagnostic criteria for vascular cognitive impairment and dementia by the International Society of Vascular Behavioural and Cognitive Disorders and World Stroke Organization (VasCog-2-WSO) used the term "Vascular Cognitive Impairment and Dementia" (VCID) to describe cognitive impairment from vascular etiologies[17]. VCID can be divided further based on dependency in daily function: *vascular dementia (VaD)* is a major vascular neurocognitive deficit that has impaired activities of daily living while *vascular mild cognitive impairment (vaMCI)* has a milder severity, not sufficient enough to interfere with independence[16,17]. Immediate or delayed cognitive deficits that occur within 3-6 months after onset of clinical stroke is defined as *post-stroke cognitive impairment (PSCI)*[18]. However, cerebral small vessel disease can also cause a gradual onset and slowly progressive dementia without history of stroke. The most updated criteria of VCID are listed in Table 2.

Table 2: The International Society of Vascular Behavioural and Cognitive Disorders working group and The World Stroke Organization (VasCog-2-WSO) criteria for Vascular cognitive impairment and dementia (VCID)

	Description
Part A	***Criteria for mild cognitive impairment and dementia***
	Mild cognitive impairment (both (A) and (B) are necessary)
(A)	Acquired decline from a documented or inferred previous level of performance in one or more cognitive domains as evidenced by the following:
	(1) Concerns of the person, knowledgeable informant or a clinician of mild levels of decline from a previous level of cognitive functioning.
	(2) Evidence of modest deficits on objective cognitive assessment based on a validated measure of neurocognitive function in ≥ 1 cognitive domain.
(B)	The cognitive deficits are *not sufficient to interfere with independence* (instrumental activities of daily living are preserved).
	Dementia (both (A) and (B) are necessary)
(A)	Evidence of substantial cognitive decline from a documented or inferred previous level of performance in one or more cognitive domains, based on:
	(1) Concerns of the person, a knowledgeable informant, or the clinician, of significant decline.

	(2) Clear and significant deficits in objective assessment based on a validated objective measure of neurocognitive function in ≥ 1 cognitive domain.
(B)	The cognitive deficits are *sufficient to interfere with independence* (at least requiring assistance with instrumental activities of daily living).
Part B	***Evidence for predominantly vascular aetiology of cognitive impairment***
(A)	**One of the following clinical features (A1 or A2)**
(A1)	The onset of the cognitive deficits is temporally related to *≥ 1 clinical stroke*. The evidence of stroke is one of the following
	(a) Documented history of a stroke, with cognitive decline temporally associated with the event.
	(b) Physical signs consistent with stroke including hemiparesis, lower facial weakness, Babinski sign, pronator drift, sensory deficit, visual field defect, pseudobulbar syndrome (supranuclear weakness, spastic dysarthria, swallowing difficulty), and cerebellar signs.
(A2)	In the absence of history of stroke, evidence of cognitive decline from *subcortical ischaemic pathology* may be associated with more gradual onset and slowly progressive course, typically predominant in some combination of attention and processing speed, and/or executive functioning.
(B)	**Presence of significant neuroimaging MRI (preferable) or CT evidence of cerebrovascular disease (at least one of the following)**
	(1) Multiple infarcts or a single extensive or strategically placed infarct (e.g., thalamus).
	(2) Multiple lacunes (≥ 2) outside the brainstem, one lacune may be sufficient if strategically placed or in combination with extensive white matter hyperintensities.
	(3) White matter hyperintensities, particularly if they are extensive and confluent.
	(4) Multiple intracerebral haemorrhages; one may be sufficient if large and/or in a lobar location or otherwise strategically placed.
Part C	***Features that may suggest an alternative or additional aetiology***
(1)	**Clinical features**
	(a) Insidious early onset of cognitive, perceptual and motor symptoms in the absence of corresponding focal vascular lesions (infarct or small vessel disease) on brain imaging or history of vascular events.
	(b) Early and prominent movement disorder suggestive of Lewy body disease or other alpha-synucleinopathy or other non-vascular movement disorder.
	(c) Features strongly suggestive of another primary neurological disorder sufficient to explain the cognitive impairment.
(2)	**Neuroimaging**
	(a) Absent or minimal cerebrovascular lesions on CT or MRI.

(3) Biomarkers

(a) The presence of biomarkers of Alzheimer's disease, dementia with Lewy bodies, or other disease related to cognitive decline.

(Adapted from Sachdev PS et al 2025[17] and Lennon MJ and Sachdev PS 2026[19])

2.1.2 Epidemiology and risk factors

Dementia from cerebrovascular aetiology is the second leading cause of dementia syndrome which accounts for 20-40% of all dementia diagnoses[20]. Pure VaD represents approximately 15% of all dementia cases, with mixed vascular and degenerative dementia accounting for an additional 16%[21].

Regarding non-modifiable risk factors, age is the strongest risk factor for VCID, similar to neurodegenerative diseases[20]. Genetic factors have some small effects for VaD risks, mostly the Apolipoprotein E4 genotype. As for ethnicity, publications from US Medicare data have reported higher VaD prevalence for Black and Hispanic groups compared with the non-Hispanic White population[22]. There have been inconsistent results about sex differences from population-based studies. Some studies showed higher VCID prevalence and incidence in women while men might be more vulnerable to VaD. However, many studies found no difference between sexes[22].

Modifiable risk factors, mainly vascular risk factors might account for up to 40% of VaD risk at a population level[22]. Principal associated factors include hypertension, high cholesterol, diabetes mellitus, obesity, cardiac diseases (especially atrial fibrillation and ischaemic heart disease), smoking, and psychiatric diseases (especially depression and delirium) mostly in midlife[18,20].

Post-stroke cognitive impairment (PSCI) is most common in the first year after stroke with a cumulative incidence up to 60% of stroke survivors[23]. The prevalence of post-stroke dementia (PSD) varies by stroke severity and history of recurrence. Apart from vascular risk factors as in VCID, factors which are associated with severity of PSCI includes stroke type (ICH has a higher PSCI rate than ischaemic stroke), stroke location (lobar and left-sided lesions fare worse), stroke volume, pre-existing cognitive impairment, pre-existing small vessel disease, and recurrent stroke[18,24].

2.1.3 Pathophysiology

The mechanisms of VCID can be differentiated into acute and chronic phases (Figure 1):

Pre-stroke phase: Pre-existing brain pathology, including Alzheimer's disease, small vessel disease, or other neurodegenerative processes, might make patients more vulnerable to cognitive deterioration after precipitating vascular insults. In contrast, many people may have protective mechanisms to cognitive decline related to brain resilience. Brain resilience is a combination of the capacity of the brain to counteract the accumulation of injury and the compensatory mechanisms to lessen this damage including vascular remodelling, angiogenesis, and neuroplasticity[24]. High education and high socioeconomic status may promote brain resilience for patients.

Acute stroke phase: As described above, both ischaemic and haemorrhagic strokes can cause direct destruction of critical structures especially cerebral cortex, basal ganglia, and thalamus. In addition, injuries also lead to disruption of structural and functional connection of white matters. During the acute phase of stroke, secondary global brain dysfunction can happen due to acute inflammation, systemic infection, and metabolic alteration. Therefore, a large size of infarction or hematoma, lesion site in a strategic area, and complications after the acute stroke event can all result in more severe VCID[18,25].

Chronic stroke phase: Vascular injury can lead to chronic reduction of blood flow, chronic inflammation and degeneration, and accumulation of neurotoxic proteins such as fibrinogen, thrombin, as well as amyloid-beta and tau like in Alzheimer's disease[18].

Also relevant to VCID pathophysiology is the concept of the *neurovascular unit (NVU)* which consists of neurons, glial cells, blood vessels, and extracellular matrix. The NVU is theorized to integrate neuronal activity with cerebral perfusion, modulate function of blood brain barrier (BBB), and interact with extracellular matrix proteins. The NVU might underlie the pathogenesis of many central nervous system disorders[24,26].

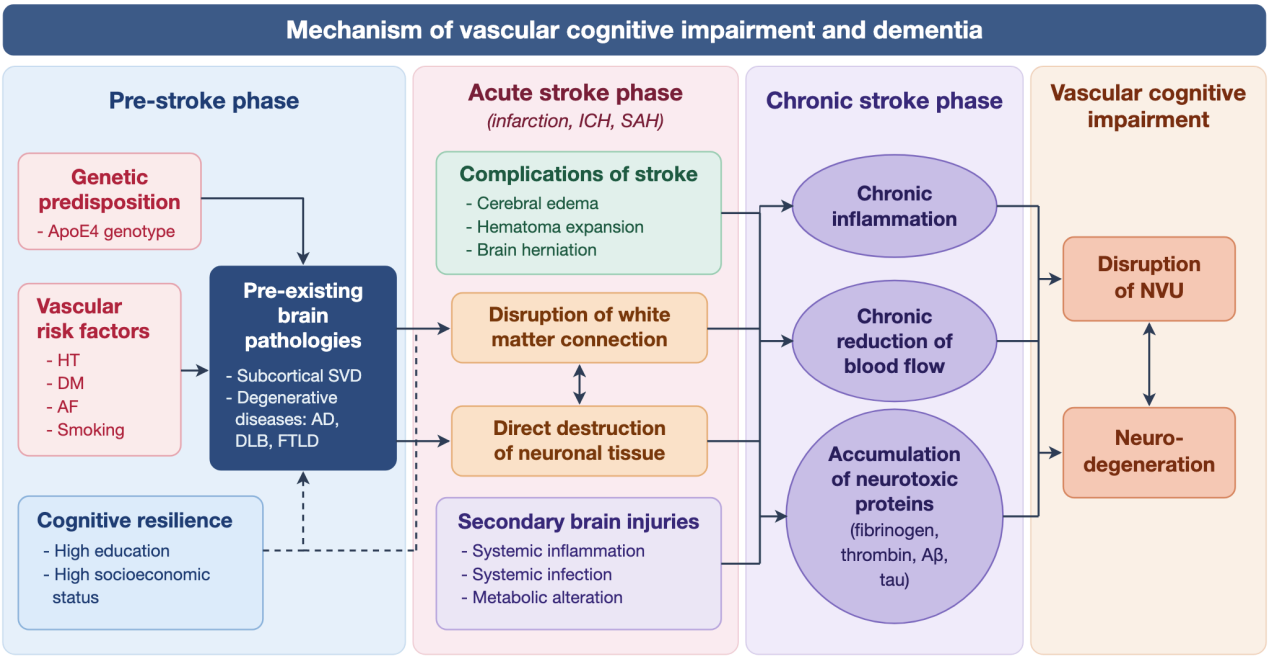


Figure 1: Mechanism of vascular cognitive impairment and dementia (VCID)

ApoE4 = apolipoprotein E4, HT = hypertension, DM = diabetes mellitus, AF = atrial fibrillation, SVD = small vessel disease, AD = Alzheimer's disease, DLB = dementia with Lewy body, FTLD = frontotemporal lobar degeneration, ICH = intracerebral haemorrhage, SAH = subarachnoid haemorrhage, Aβ = amyloid-beta, NVU = neurovascular unit

2.1.4 Presentation and course of illness

Types of vascular dementia can be categorized based on different mechanisms as table 3[27-29].

Disease courses of VCID vary according to disorder types. Multi-infarct dementia and strategic infarct dementia, also classified as PSCI, tend to manifest as abrupt cognitive decline after stroke with stepwise progression as multiple episodes of stroke occur. On the other hand, subcortical small vessel disease dementia may not result in clinical stroke and often manifests with insidious onset and gradual progression of cognitive deterioration[30].

Table 3: Types of vascular dementia and their presentations

Types	Clinical presentations
1. Subcortical small vessel disease dementia	- The most common type which manifests on neuroimaging as lacunes, white matter hyperintensity, and cerebral microbleeds. - Cognitive manifestations usually involve executive dysfunction, impaired processing speed, impaired complex attention, apathy, mood disorders, and emotional lability due to the disruption of fronto-subcortical white matter circuits by small vessel disease. - Common accompanying neurological signs and symptoms include gait difficulty, psychomotor slowing, and urinary incontinence.
2. Multi-infarct dementia	- Larger size and a greater number of infarctions are associated with worse cognitive outcomes. - Symptoms are varied according to the brain regions affected by vascular lesions; examples include aphasia (in left peri-Sylvian area lesions), visuospatial dysfunction (in bilateral occipitotemporal or occipitoparietal lesions), and executive dysfunction (in frontal lobe lesions). - Asymmetrical signs of stroke including focal weakness and numbness, facial palsy, dysarthria, unilateral incoordination, and asymmetrical reflexes can help support the diagnosis.
3. Strategic-infarct dementia	- A single small infarction can cause severe cognitive impairment when occurring in strategic location. - Typical strategic areas include the left angular gyrus, thalamus, basal forebrain, caudate, putamen, and hippocampus. - The nature of cognitive problems again relates to lesion sites; for example, anterior thalamic lesions primarily result in memory deficits whereas left angular gyrus lesions result in features of Gerstmann syndrome (dysgraphia, acalculia, left-right disorientation, finger agnosia), as well as ideomotor apraxia and anomic aphasia.
4. Haemorrhagic dementia	- Macrohaemorrhages including both ICH and SAH can cause severe cognitive decline. - Several studies have also suggested that accumulation of more than 3-5 cerebral microbleeds increases risk of cognitive deficits[28,29]
5. Mixed dementia	- Pre-existing degenerative diseases, mainly Alzheimer's disease, may cause synergistic effects to aggravate cognitive impairment in VCID patients. - Patients usually manifest more severe cognitive decline than pure VCID cases.

(Adapt from Dichgans et al 2017[27])

2.1.5 Assessment and investigation

1) Cognitive screening: Because VCID and PSCI affect both functional recovery after stroke and overall quality of life, cognitive screening using neuropsychological tests is necessary[24,31,32]

- *Pre-stroke cognitive function:* Many screening tools can assess subjective cognitive profiles before a stroke event in PSCI patients including the National Adult Reading Test (NART)[33] and the Informant Questionnaire on Cognitive Decline in Elderly (IQCODE)[34].

- *Early post-stroke period:* Brief screening tests in the recovery phase during hospitalization can indicate patients-at-risk who could have PSCI in the future. The Mini Mental State Examination (MMSE)[35] and Montral Cognitive Assessment (MoCA)[36] are suitable in the busy setting of stroke units. The MoCA might be better in detecting executive dysfunction and processing speed problems in stroke patients[37].

- *Late post-stroke period and VCID screening in the clinic:* The MoCA and Addenbrooke's cognitive examination III (ACE-III)[38] testing are reasonable methods for cognitive screening in clinic settings. Extensive neuropsychological batteries can be used to add more detailed information about each cognitive domain.

- *Exclusion of other conditions:* Many reversible conditions can interfere with cognitive ability including depression, delirium, and apathy.

As for patients in whom cognitive testing cannot be performed, ascertainment of cognitive impairment and dementia can still be made using combinations of cognitive symptom assessments reported by informants (e.g. IQCODE, Ascertain Dementia 8 Questionnaire; AD8[39]) and assessments of cognitively relevant daily activities (e.g. Lawton-Brody Instrumental Activities of Daily Living Scale)[40].

2) Blood tests: Baseline basic blood tests should be done in all suspected VCID patients to exclude reversible causes and assess individual vascular risk factors including complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, magnesium, glucose, lipid profile, haemoglobin A1C, thyroid function tests (mainly thyroid stimulating hormone), liver function tests, and vitamin B12 level. Additional blood tests can be considered on a case-by-case basis including HIV serology, syphilis testing, erythrocyte sedimentation rate, C-reactive protein, and homocysteine level[7,41].

3) Neuroimaging is very important for every case and is included in all diagnostic criteria of VCID.

- *Brain computerized tomography (CT)* is widely available and very quick to perform[18]. It can detect multiple, strategic-located, or lacunar infarction and exclude most ICH or SAH effectively.

- *Brain magnetic resonance imaging (MRI)* is the most informative method for structural evaluation. It provides more details of small vessel disease features including small subcortical infarcts, small lacunes, white matter hyperintensities, enlarged perivascular spaces, both cortical and subcortical cerebral microbleeds, and cortical superficial siderosis (which indicates previous small SAH) which cannot be assessed by CT[18,42]. Whereas white matter hyperintensities can be seen in older patients with normal cognition, increasing white matter hyperintensity volume or visually rated burden such as using the Fazekas scale is strongly associated with cognitive decline

(Figure 2)[43-45]. MRI can also help evaluate global and regional brain atrophy patterns associated with both small vessel disease and neurodegenerative pathologies.

- *Positron emission topography (PET):* In patients with insidious cognitive decline, fluorodeoxyglucose-positron emission tomography (FDG-PET) can help differentiate scattered areas of focal cortical and subcortical hypometabolism in VCID that differ from the typical cortical hypometabolic pattern of Alzheimer's disease in association cortices. However, the former pattern is not specific to VCID and can be found in other neurological disorders. There are also various amyloid- and tau-tracer PET scans which can be used to diagnose pre-existing Alzheimer's pathology, although availability remains limited[46].

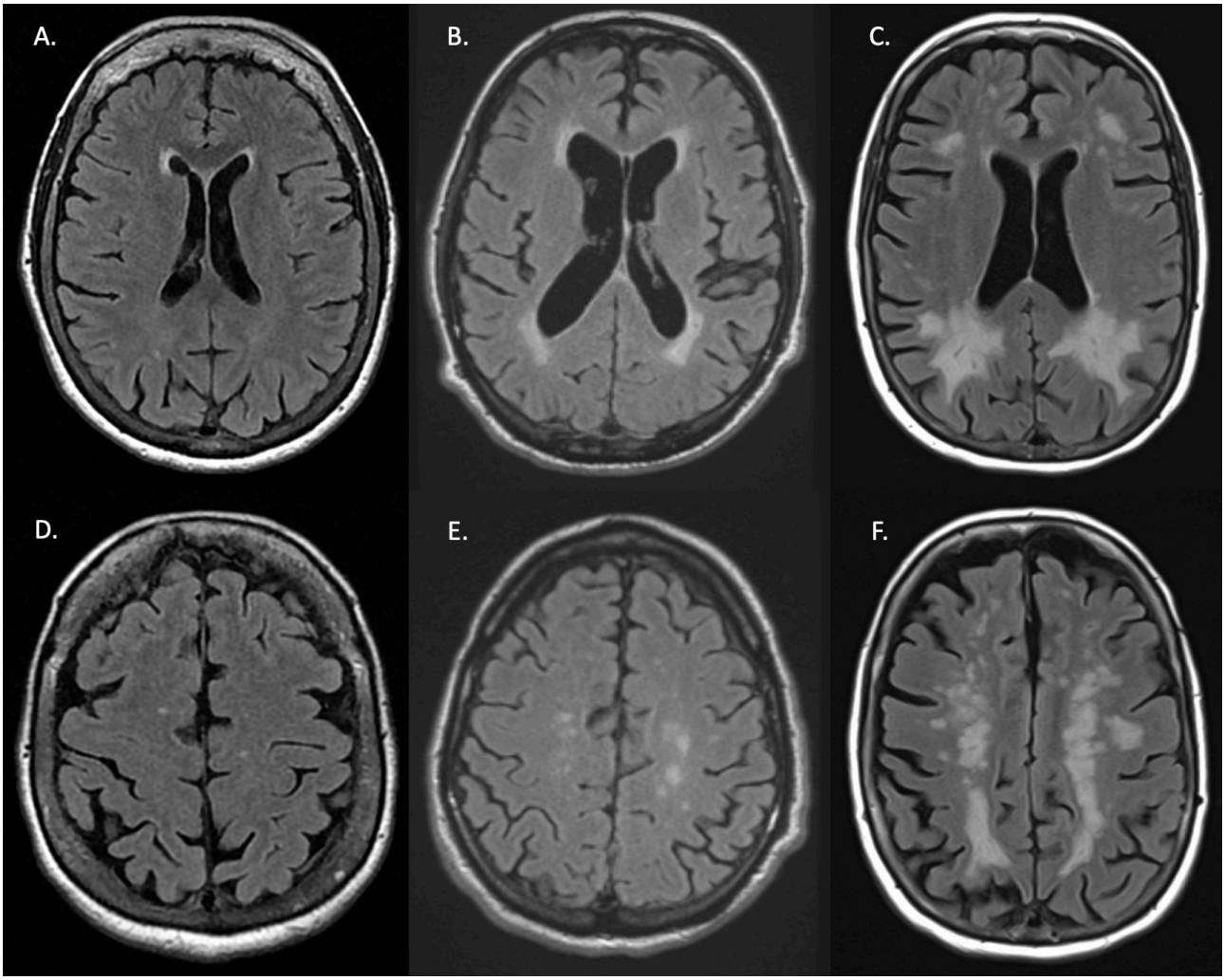


Figure 2: Magnetic resonance imaging (MRI) of the brain showing subcortical small vessel disease burden categorized by Fazekas scales.

Brain MRI, T2 weighted-Fluid Attenuated Inversion Recovery (T2W-FLAIR) axial view. A 76-year-old woman with Fazekas scale 1 (Figure A, D). Figure A shows cap appearance of periventricular white matter hyperintensity (WMH) and Figure D shows subcortical small punctate foci. A 76-year-old man with Fazekas scale 2 (Figure B, E). Figure B presents periventricular WMH smooth halo and Figure E features the beginning of confluence WMH. A 71-year-old woman with Fazekas scale 3 (Figure C, F). Figure C indicates periventricular lesions extending into deep white matter and Figure F shows large confluent WMH.

4) Fluid biomarkers: Serum neurofilament light chain (NfL), a marker for axonal degeneration, has been found to correlate with widespread white matter changes after stroke and may predict post-stroke cognitive and functional status[18], but this marker is not specific to VCID. Recent progress in Alzheimer's disease-specific biomarkers including plasma-based amyloid and phosphorylated tau markers offers more convenient methods to identify Alzheimer's disease or support mixed dementia diagnosis in patients with suspected VCID[18].

2.1.6 Treatment

Treatment approaches for VCID can be differentiated into pharmacological and non-pharmacological treatments.

1) Pharmacological treatment: While there are currently no US Food and Drug Administration (FDA)-approved drugs for VCID, Cholinesterase Inhibitors and/or Memantine are approved for use in several jurisdictions.

- *Cholinesterase inhibitors:* Because acetylcholine level and choline acetyltransferase activity are decreased in patients with AD and VCID, cholinesterase inhibitors, which increase acetylcholine in the synaptic cleft, may provide benefits for symptomatic cognitive treatment. A Cochrane meta-analysis found that donepezil 10 mg appears to have the highest benefit followed by Galantamine 16-24 mg[47]. Cholinesterase inhibitors also have evidence of benefits in subcortical small vessel disease more so than in multi-infarction dementia[19].

- *Memantine:* Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that can enhance neuronal long-term potentiation by reducing excitotoxic damage. A Cochrane meta-analysis found a small clinical benefit with memantine 20 mg daily for cognitive function[48].

2) Non-pharmacological and risk factor management: *Vascular risk factors* such as hypertension, diabetes mellitus, dyslipidaemia, cardiac disease, and smoking should be managed appropriately to reduce risks of recurrent stroke and subsequent cognitive deterioration[19,32]. *Physical and cognitive rehabilitation* can also provide modest improvements for cognition. Multi- and single-domain interventions are associated with improvements in composite global cognition for patients with mild to moderate VCID and AD[32,49]. *Other important management strategies* include educational activities, tailor-made environmental support for patients, safety management including appropriate housing modifications and driving restrictions, occupational therapy, and caregiver support.

2.1.7 Prevention

Control of vascular risk factors is the most important preventative strategy for both post-stroke patients and patients-at-risk with cerebral small vessel disease. These strategies are summarized in table 4[18,19,32,50,51].

There have been many studies integrating multidomain lifestyle interventions for dementia prevention. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study team targeted dementia risks through five intervention pillars (diet guidance, physical activity, cognitive training, social activities, vascular and metabolic monitoring)[52]. In addition, the United States of America Study to Protect Brain Health Through Lifestyle Intervention to Reduce

Risk (US POINTER) used four pillars for prevention strategies (physical exercise, nutrition, cognitive and social exercise, and health monitoring) as multimodal intervention[53]. Both studies showed significant improvements of overall cognitive performance in intervention groups.

Table 4: Preventative strategies for vascular cognitive impairment and dementia

Risk factors	Management
1. Hypertension	- Hypertension treatment with antihypertensive drugs significantly reduces the risks of vascular and overall dementia. - The advantage of standard (keeping BP 130-140 mmHg) versus more intensive (keeping BP < 120 mmHg) blood pressure therapy is still inconclusive.
2. Diabetes mellitus	- Type 2 diabetes is a strong risk factor for both PSCI and subcortical VCID. However, the effects of different types of diabetes medications on VCID are still unclear. - *Metformin* has been found to have inconsistent benefits. - Newer agents such as *glucagon-like peptide-1 (GLP-1) receptor agonists* and *sodium-glucose transport protein-2 (SGLT-2) inhibitors* have recently shown promise for VCID prevention[19,32].
3. Dyslipidaemia	- There is no direct evidence that supports the use of statins to decrease risk of VCID. - However, *lipid-lowering agents* can prevent subsequent stroke, which is a strong risk factor for PSCI. Therefore, lipid and cholesterol treatment should be provided following treatment guidelines appropriately.
4. Antiplatelets and anticoagulants	- Current guidelines favour long-term single antiplatelet therapy for VCID prevention. - Indications for *antiplatelet* use should comply with guidelines for secondary stroke prevention. - Given the strong stroke risk with atrial fibrillation, *anticoagulant treatment* in atrial fibrillation has been found to significantly reduce risk of dementia[50].
5. Healthy lifestyle interventions	- *Smoking cessation* is necessary for secondary stroke prevention. - *Alcohol cessation* or limitation to < 14 units/week can also reduce some risks of cognitive decline. - *Other lifestyle factors* that can reduce cognitive risk include regular physical activity, eating brain-healthy diets like the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND), cognitive stimulation activities, and social engagement[51].

2.2 Post-stroke depression

2.2.1 Definition

Post-stroke depression is defined as a depressive disorder that develops following a cerebrovascular event[54]. Post-stroke depression is not simply a reactive type of depression, resulting from the psychological stress of suffering a stroke, but a neuropsychiatric syndrome, which results from the interplay of multiple biological and psychosocial factors[55,56].

2.2.2 Epidemiology

Post-stroke depression is a common neuropsychiatric manifestation of stroke, affecting approximately 25 to 35% of patients within the first year of stroke. However, the prevalence rates may vary over time, with post-stroke depression seen in about 28% of patients in the first month and 30% of patients in the first year after stroke, but may ultimately affect up to 50% of stroke survivors at some point during their recovery[57].

Risk factors include pre-morbid depression, coexisting physical disability, coexisting cognitive impairment, low social support, as well as greater stroke severity. Although some studies have associated post-stroke depression with female gender and younger age, this evidence remains inconsistent[55].

2.2.3 Etiopathology

The aetiology of post-stroke depression includes neurobiological mechanisms as well as multiple psychosocial factors such as adjusting to disability, loss of independence, social isolation, and contributions from pre-morbid depression and personality traits. The primary neurobiological mechanism considered in the pathophysiology is the disruption of frontal-subcortical circuits, especially the connections between the lateral prefrontal cortex, anterior cingulate cortex, and subcortical structures like the basal ganglia, thalamus and their connections which impairs emotional processing and regulation[58]. Dysregulation of mono-aminergic neurotransmitter systems[59], chronic CNS inflammation and reduced neuroplasticity have also been proposed as contributors[60].

2.2.4 Clinical presentation

Post-stroke depression is characterised by low mood, anhedonia, fatigue, sleep disturbances, and reduced concentration, which generally coexist with neurological deficits. Post-stroke neurological deficits may complicate the diagnosis and it is important to differentiate (or at least attempt to differentiate) the somatic symptoms, such as psychomotor slowing or fatigue which may occur due to the stroke, from the features of post-stroke depression[59].

Individuals with post-stroke depression may also present with increased irritability, anxiety, emotional lability, and diminished motivation, which follow variable trajectories and may be transient, persistent, or recurrent. Without proper management, post-stroke depression can result in delayed functional recovery, increased disability and mortality[61].

2.2.5 Assessment and diagnosis

An important step in the diagnosis of post-stroke depression is to differentiate it from apathy and fatigue, which can coexist with depression in cases of stroke or vascular cognitive impairment. The key clinical features that help in this differentiation are the feeling of sadness, anhedonia, hopelessness, and guilt, which are characteristic of depression rather than of apathy or fatigue[59].

Common screening tools for PSD include Patient Health Questionnaire 9 (PHQ-9)[62,63], Hamilton depression rating scale[64], and geriatric depression scale (GDS)[65].

2.2.6 Management

The management of post-stroke depression primarily relies on the use of selective serotonin receptor inhibitors (SSRI) like sertraline, citalopram, and escitalopram. Although these medications are generally well tolerated, it is important to monitor the patient for important side-effects of these like hyponatraemia, QTc prolongation, and sedation in some cases[57,66].

There is also a role for non-pharmacological interventions such as cognitive-behavioural therapy, problem solving therapy, behavioural activation, and other rehabilitation strategies like social support which may help in enhancing recovery in such patients[67].

2.3 Post-stroke Apathy

2.3.1 Definition

Apathy is defined as a syndrome of diminished motivation with development of reduced goal-directed thought, feeling, and behaviour. It is primarily characterised by lack of energisation, the neuroanatomical substrate of which is the anterior cingulate cortex and its subcortical connections which are involved in motivation and reward processing[68].

2.3.2 Epidemiology

The prevalence of post-stroke apathy is ranges from 20 to 40%[69]. The predominant risk factors reported are older age, depression, increased disability, medical comorbidities, and presence of cognitive deficits[70,71].

2.3.3 Pathophysiology

The primary pathophysiological mechanism for apathy is the disruption of frontal-subcortical circuits involving the anterior cingulate cortex, dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, and ventromedial prefrontal cortex, and their connections with the basal ganglia and thalami; lesions in any of these structures have been reported to cause apathy[58,68,72]. However, apathy has also been reported with some cases of pontine infarcts[73]. Three main frontal-subcortical circuits have been described in relation to apathy, namely the “Emotional-affective” apathy circuit (for reward processing), “Cognitive” apathy circuit (goal-directed behaviour), and the “Auto-activation” deficit circuit (behavioural initiation)[74-76]. The primary dysfunction in such cases is that of the dopaminergic circuits, which are essential for motivation and reward processing.

2.3.4 Clinical presentation and natural course

The important clinical features of post-stroke apathy are lack of initiative, diminished interest, reduced emotional responsiveness, and decrease engagement in activities. Patients with apathy tend not to voice their symptoms, consequently, it often goes undiagnosed. It is important to differentiate apathy from depression, which is defined as presence of persistent and excessive sadness,

guilt, and hopefulness for most of the day, nearly every day (formally defined as a duration of at least two or more weeks). Patients with depression generally have a negative self-perception while patients with apathy often report that they are feeling fine despite their obvious functional decline[77,78]. Another important differential diagnosis is anhedonia, which is defined as loss of interest in previously pleasurable activities. Although both may co-exist, in such isolated cases of anhedonia, there is no loss of goal-directed behaviour or reactive emotion, unlike apathy. Post-stroke apathy has been associated with poor functional outcomes, reduced rehabilitation participation, and increased caregiver burden[69].

2.3.5 Assessment

The primary tools for assessment of apathy include the Starkstein Apathy Scale and the Apathy Evaluation Scale[68,79]. It is important to evaluate the patient for post-stroke depression as well using the instruments described above, given the importance of distinguishing depression from apathy. Brain imaging like CT or MRI scans may also help in the localisation of the apathy-associated lesion in such cases.

2.3.6 Management

The primary approach to the management of apathy is non-pharmacological, including measures like behavioural interventions/rehabilitation, occupational therapy, caregiver education, physical exercise programs, and environmental modification[77,80].

Apathy is one of the most difficult symptoms to manage among the neuropsychiatric symptoms of stroke. As of now, there is no approved medication for apathy[81]. Off-label pharmacological management approaches that are used in practice include drugs like methylphenidate, modafinil, amantadine, and dopaminergic agents, though there is inconsistent evidence regarding their effectiveness[82]. There may be a benefit from using antidepressants in these patients if there is a coexisting or underlying depression, but these drugs have also been reported to cause worsening of apathy in some cases[83].

2.4 Post-stroke mania

Post-stroke mania is a relatively uncommon manifestation of stroke, with an estimated prevalence of around 2% among stroke survivors[57]. It is primarily caused by lesions of the right hemisphere, particularly when involving areas like the orbitofrontal cortex, thalamus, and basal ganglia[84]. Such lesions are thought to cause the loss of free control over the left-hemispheric mood-elevating areas[84,85]. Although there are a limited number of case reports that have been published on post-stroke mania, it has been observed that it affects males more than females.

Characteristic clinical features include an elevated or irritable mood, decreased need for sleep, pressured speech, delusions of grandiosity, and disinhibition. It is important to differentiate this condition from delirium and medication-induced altered mental states. Additionally, it is important to recognise it at the earliest as mania may cause challenging behavioural disturbances, poor judgement, impulsivity, and reduced treatment adherence. The primary clues to the diagnosis include mania

developing for the first time in later life and in close temporal association with stroke, in the presence of focal neurological deficits or vascular risk factors.

Assessment should include a proper psychiatric history, with evaluation of any family history of bipolar disorder, timeline relative to stroke onset, collateral information, cognitive assessment, and neurological examination, along with screening for delirium and reversible contributors like infection.

Management primarily includes the use of mood stabilisers and atypical antipsychotics, valproate, and lithium[85]. However, these agents should be cautiously given, as they may lead to delirium and rarely cardiac side-effects[86,87].

2.5 Post-stroke psychosis

Post-stroke psychosis is a relatively uncommon manifestation, with a reported prevalence of 3-7% among individuals after a stroke[88-90]. Men may be slightly over-represented[89]. Post-stroke psychosis is associated with lesions of the right hemisphere, especially in the fronto-temporal regions. It has major clinical implications including poor functional recovery, prolonged hospital stays, increased caregiver burden, and long-term mortality[89,91]. One should be careful not to mistake it for confusion, dementia, or emotional stress[92].

Post-stroke psychosis refers to the emergence of hallucinations, delusions, or other psychotic symptoms in a patient with stroke, without any pre-morbid history of psychosis. Although symptoms may occur immediately after stroke, presentation after a period of months is not uncommon[90].

Multiple mechanisms have been proposed including evolving salience network dysfunction, diaschisis, maladaptive neuroplasticity, neuroinflammation, and neurotransmitter changes[89,92,93]. The major anatomical correlates are the right frontal lobe, right temporal lobe, right orbitofrontal cortex, right caudate nucleus, and thalamus[88,89]. Another proposed mechanism is that the right hemisphere lesions impair belief evaluation systems, allowing impossible interpretations to persist[94].

The most important clinical features of post-stroke psychosis are delusions, hallucinations, paranoia, and, rarely, misidentification syndromes. Although the clinical phenotype is heterogenous, the most common syndromes reported are delusional disorder and schizophrenia-like psychosis[89]. However, unlike schizophrenia, these patients mostly do not present with “negative” symptoms, chronic thought disorder, or long premorbid decline.

Management primarily relies on low-dose, atypical antipsychotics like risperidone, quetiapine, and sometimes haloperidol, as well as rehabilitation. It is also important to distinguish this entity from delirium, which may coexist with the stroke. The prognosis of post-stroke psychosis is generally poor compared to stroke patients without psychiatric illness[90,95].

2.6 Emotional lability and pseudobulbar affect

Pseudo-bulbar affect, post-stroke emotionalism, or emotional lability after stroke is defined as involuntary episodes of laughing or crying that are disproportionate or incongruent with the underlying mood[96,97]. The clinical significance of this entity lies in the fact that it can cause embarrassment, social withdrawal, caregiver

distress, and hinder the post-stroke rehabilitation process. It may be mistaken for depression or other psychiatric illness although they can coexist simultaneously[98].

The core clinical feature is paroxysmal emotional expression which may be precipitated by trivial stimuli or provoking factors, but in some cases, it may occur without any provoking factor. The episodes are exaggerated and inappropriate to the context or to the patient's internal mood. Crying episodes are more frequently reported than laughing episodes and the patients find these events unwanted and difficult to suppress. The distinguishing feature of pseudobulbar affect compared to other affective disorders is that it is characterised by a dysregulation of emotional expression rather than a mood disturbance[98].

The reported prevalence of the entity (when inclusively defined) ranges from 10 to 20% of stroke patients[99,100]

The primary dysfunction is the disruption of corticobulbar and fronto-pontine pathways, which causes disinhibition of emotional expression[101]. Structures that are involved are the prefrontal cortex, involved in voluntary emotional regulation; the limbic region, important for emotional response; basal ganglia and thalamus, involved in the modulation of effective motor output; brainstem, for facial and vocal expression; and the cerebellum, for emotional modulation and timing.

Some studies have found an association between emotional incontinence and executive dysfunction, indicating that the disruption of frontal control systems may lead to dysregulation of emotional expression[102].

Several scales can be used to evaluate emotional lability, the most important of which is the Centre for Neurological Study Lability Scale (CNSLS)[103].

The primary management approach includes the use of SSRIs, tricyclic antidepressants, and dextromethorphan/quinidine, with some patients showing rapid improvement with these medications[104-106]. A Cochrane review updated in 2022 found that although antidepressants reduce the frequency and variety of post-stroke emotionalism, the certainty of evidence was very low to moderate as the trials were very small and had important methodological limitations[107].

Chapter Summary

- Cerebrovascular disease is one of the leading causes of cognitive impairment and can lead to multiple neuropsychiatric complications.
- Vascular cognitive impairment and dementia (VCID) is generally characterised by executive dysfunction, slow processing speed, and impaired attention, especially in the case of small vessel disease.
- The cornerstone of VCID management are secondary prevention and control of vascular factors while pharmacological therapy like cholinesterase inhibitors and memantine may provide modest symptomatic benefit in selected patients.
- Post-stroke depression is a common neuropsychiatric complication which affects one-third of stroke survivors. The pathogenesis involves alterations in frontal subcortical circuits, monoaminergic dysfunction, neuroinflammation, and psychosocial stressors.
- Post-stroke apathy is an under-recognized complication of stroke characterised by reduced motivation and goal-directed behaviour.
- Emotional lability or pseudobulbar affect occurs due to the disruption of cortico-bulbar and fronto-cerebellar circuits, leading to involuntary laughing or crying episodes, which are incongruent with the patient's emotional state.
- The management of post-stroke neuropsychiatric complications involves multidisciplinary treatment, which requires both pharmacological and non-pharmacological approaches, including vascular risk factor control, rehabilitation, psychological therapy, caregiver education, and cognitive interventions.

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