Title: Post-Stroke Cognitive Impairment and Dementia

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Abstract

Post-stroke cognitive impairment and dementia (PSCID) is a major source of morbidity and mortality after stroke worldwide. PSCID occurs as a consequence of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage. Cognitive impairment and dementia manifesting after a clinical stroke is categorized as vascular even in people with comorbid neurodegenerative pathology, which is common in elderly individuals and can contribute to the clinical expression of PSCID. Manifestations of cerebral small vessel disease, such as covert brain infarcts, white matter lesions, microbleeds, and cortical microinfarcts are also common in stroke patients and likewise contribute to cognitive outcomes. While studies of PSCID historically varied in the approach to timing and methods of diagnosis, most of them demonstrate that older age, lower educational status, socioeconomic disparities, premorbid cognitive or functional decline, life-course exposure to vascular risk factors and a history of prior stroke increase risk of PSCID. Stroke characteristics, in particular stroke severity, lesion volume, lesion location, multiplicity and recurrence, also influence PSCID risk. Understanding the complex interaction between an acute stroke event and pre-existing brain pathology remains a priority and will be critical for developing strategies for personalized prediction, prevention, targeted interventions, and rehabilitation. Current challenges in the field relate to a lack of harmonization of definition and classification of PSCID, timing of diagnosis, approaches to neurocognitive assessment, and duration of follow-up after stroke. However, evolving knowledge on pathophysiology, neuroimaging, and biomarkers offers potential for clinical applications and may inform clinical trials. Preventing stroke and PSCID remains a cornerstone of any strategy to achieve optimal brain health. We summarize recent developments in the field and discuss future directions closing with a call for action to systematically include cognitive outcome assessment into any clinical studies of post-stroke outcome.

Non-standard Abbreviations and Acronyms

AD– Alzheimer's Disease

ADAS-Cog – the Alzheimer's Disease Assessment Scale-Cognitive Subscale

AGES - Age, Gene/Environment Susceptibility Reykjavik Study

Aβ - amyloid beta protein

APOE - apolipoprotein E

AF – atrial fibrillation

ASPIS - Austrian Polyintervention Study to Prevent Cognitive Decline after Ischemic Stroke study

BBB – blood-brain barrier

BP – blood pressure

CSN - Canadian Stroke Network

CAM - the Confusion Assessment Method CSF – cerebrospinal fluid

CogFAST - Cognitive Function after Stroke study

DEMDAS - The Determinants of Dementia After Stroke Study

DISCOVERY – the Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on Recovery studY

DM – diabetes mellitus

DSM - Diagnostic and Statistical Manual of Mental Disorders

DTI – diffusion tensor imaging

GWAS – genome-wide association study

HBC - The Heart-Brain Connection study

HS – hemorrhagic stroke

ICD - International Classification of Diseases

ICH – intracerebral hemorrhage

IS – ischemic stroke

ISGC – International Stroke Genetics Consortium

J-STAR - Japan Statin Treatment Against Recurrent Stroke trial

LAST - Life After Stroke Trial MCI – mild cognitive impairment

MoCA – the Montreal Cognitive Assessment test

MMSE - the Mini-Mental State Exam

MRI – magnetic resonance imaging

NCD – neurocognitive disorder

NFL - neurofilament light chain

NICE - Nimodipine In preventing Cognitive impairment in ischemic cerebrovascular Events trial

NIH – National Institutes of Health

NIHSS - National Institutes of Health Stroke Scale

NINDS - National Institute for Neurological Disorders and Stroke

NMDA - N-Methyl-D- aspartate

NVU – neurovascular unit

OSC - Oxford Cognitive Screen

OXVASC –Oxford Vascular *S*tudy

PET – positron emission tomography

PRoFESS – Prevention Regimen for Effectively Avoiding Second Strokes trial

PROGRESS - Perindopril Protection Against Recurrent Stroke Study

PSCI – post-stroke cognitive impairment

PSCID - post-stroke cognitive impairment and dementia

RCT – randomized clinical trial

REGARDS - The REasons for Geographic and Racial Differences in Stroke study

SAH - aneurysmal subarachnoid hemorrhage

SPS3 - Secondary Prevention of SubCortical Stroke Study

STROKOG - Stroke and Cognition Consortium

SVD – small vessel disease

SVDs@target - Small Vessel Diseases-at-target consortium

TIA – transient ischemic attack

VCI – vascular cognitive impairment

VCID – vascular cognitive impairment/dementia

WMH – white matter hyperintensities

Introduction

Stroke remains a leading cause of disability in the United States and around the world.[1,2] The development of effective acute treatments has resulted in global trends showing improvement in stroke outcomes.[3–5] Yet, post-stroke cognitive impairment and dementia (PSCID) remain highly prevalent and disabling.[6–10] Cognitive deficits are present in over 70% of stroke survivors, depending on stroke type, definition, and timepoint of assessment,[8,11] (**Table 1**) and are associated with disability,[12,13] dependency,[14] and morbidity;[15,16] thus, posing a major burden to patients, caregivers, and healthcare systems. As such, there is a critical need for an accurate diagnosis, timely intervention, and optimal prevention of PSCID.

PSCID may occur as a consequence of acute ischemic stroke (IS),[17], as well as intracerebral hemorrhage (ICH),[18–20] and aneurysmal subarachnoid hemorrhage (SAH)[21,22] (**Figure 1**). There is growing recognition that the risk and temporal trajectory of PSCID is determined by an interplay of multiple factors including modifiable and non-modifiable risk factors, co-morbidities, index stroke characteristics (e.g. ischemic versus hemorrhagic), features of the acute infarct or hemorrhage (e.g. size, location, multiplicity), and the overall burden of pre-existing brain injury[9,23–25] - aspects that will be discussed in detail below.

Given the frequency and variety of factors that are implicated in initiating or accelerating cognitive dysfunction in elderly people, understanding the underlying mechanisms of PSCID is of paramount significance if we are to develop accurate prediction models and effective treatments.[25,26] Acute ischemic or hemorrhagic insults to a brain with pre-existing microvascular or neurodegenerative disease can initiate a series of pathological events leading to variable trajectories of cognitive decline (**Figure 1**).[24,27] Still, the relative contributions of vascular and neurodegenerative disease to PSCID largely vary between subjects and are often difficult to determine.[28,29] Also, lack of consensus on how and when to diagnose PSCID following an acute stroke[27,30–32] has posed challenges for research and providing guidance to clinicians. Below, we review the current concept of PSCID with an emphasis on aspects relevant to diagnosis, prevention, and management.

Definition and clinical features

Post-stroke cognitive impairment (PSCI) encompasses cognitive impairments manifesting in the 3-6 months after incident stroke. It includes not only deficits specific to the stroke lesion site, such as aphasia or memory deficits, impairments arising from “strategic” infarcts in the hippocampi, thalami, and key cortical regions,[33] but also those that may have preceded the stroke. Higher-order visuospatial, attentional, and executive dysfunction, which are more associated with canonical vascular cognitive impairment (VCI), are frequently detected on post-stroke cognitive screening. Hence, PSCI is often conflated with VCI. Some researchers use the terms early and late (or delayed) PSCID to differentiate the cognitive deficits detected in the immediate post-stroke period from those that develop over the proceeding months.[34] However, these distinctions are arbitrary and poorly defined. While this is not problematic when explaining the nature of the deficits in a clinical setting, the lack of consensus in terms of disease definition (e.g. the inclusion of cases with transient ischemic attack, prior stroke, or pre-existing dementia) has impeded PSCID research.

Vascular risk factors confer both increased risk of stroke and cognitive impairment, and community-based studies of individuals having serial cognitive testing before and after incident stroke revealed increased cognitive impairment prior to their stroke as well as accelerated cognitive decline afterwards.[27,35] The last two decades have seen a concerted effort to harmonize

the description and testing of PSCID,[23,36] but more work needs to be done to improve crosstalk between the fields of stroke and cognitive neurology. Current terms are dependent on the patient's individual cognitive trajectory and impose arbitrary divisions between post-stroke cognitive deficits directly related to the acute brain lesion, cognitive impairments that may be extant years after stroke, and more diffusely defined post-stroke dementia, where cognitive *decline* is required to occur within a predefined time period following the stroke.

Classification and diagnostic criteria

PSCI has been defined as *"all problems in cognitive function that occur following a stroke, irrespective of the [stroke] etiology"* [23]. In contrast, post-stroke dementia is defined as "*immediate and/or delayed cognitive decline that begins within 6 months after a stroke and that does not reverse [encompasses dementia that develops within 6 months of stroke in patients]".*[36] Even the terms used to describe cognitive disorders due to vascular etiologies differ. Diagnostic and Statistical Manual of Mental Disorders (DSM)-V used the terms mild and major neurocognitive disorder (NCD);[37] the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG)[38] and the Vascular Impairment of Cognition Classification Consensus Study (VICCS)[36] guidelines use Mild Vascular Cognitive Disorder and Vascular Dementia or Major Vascular Cognitive Disorder; and the International Classification of Diseases (ICD)-10[39] does not include a specific definition of either PSCI or VCI but includes a definition of vascular dementia. Only the VICCS guidelines specify post-stroke dementia as a subtype of major VCI, and none use the term "PSCI" explicitly. VCI criteria perhaps better encompass the spectrum of cognitive disorders associated with all forms of cerebral vascular brain injury.[36,38,40] The lack of consensus has been identified as an obstacle to accurate prevalence[41] and cognitive trajectory[11] estimation.

Cognitive profile

Deficits related to the incident stroke are heterogenous, with lesion-specific impairments often being superimposed on impairments resulting from more diffuse vascular brain injury.[42] Domain-specific impairments resulting from the acute insult include disorders of attention such as neglect in patients with right hemispheric stroke,[43] aphasia syndromes arising from lesions in language networks, and memory impairments, most prominent in insults affecting paramedian thalami.[33,33] These may be differentiated from the underlying cognitive profile of VCI, which is characterized by attentional, executive, and visuospatial dysfunction, and by slowed processing speed. These impairments likely arise as vascular pathological brain burden. Especially white matter dysfunction,[44] disproportionately impacts widely distributed brain networks such as attention and visuospatial function.

While post-stroke delirium is a common clinical occurrence,[45] its association with future PSCID is not well understood. Post-stroke delirium can take months to resolve, and most neuropsychologists defer assessment until at least 3 months following inpatient delirium, making a temporal association difficult. Many researchers regard post-stroke delirium as evidence of pre-existing cognitive impairment, and posit that it is associated with increased risk of post-stroke cognitive decline.[46] Acute stroke lesion topography may also be linked to post-stroke delirium risk, with lesions in supratentorial regions and those supplied by the anterior circulation having higher rates of post-stroke delirium diagnosis.[47] Although, the most recent European Stroke Organisation joint guidelines found limited evidence for any clinical prediction tools for PSCI or delirium.[23] Furthermore, the presence of delirium further confounds any diagnosis of PSCID.

Time-course

Cognitive performance is dynamic due to the duelling effects of native mechanisms of recovery, secondary neurodegeneration, and recurrent cerebrovascular events. For most published

studies, cognitive impairment has been examined at a single timepoint after stroke; [11,41] thus, there are surprisingly few longitudinal studies of post-stroke cognitive trajectories. Overall cognitive performance may stabilise over the initial 12 months, and there is evidence that both genetic[48,49] (APOE e4 carrier status) and stroke factors, most prominently stroke severity,[50] mediate post-stroke cognitive trajectories. Verbal memory and processing speed appear to decline in stroke survivors. Interestingly, visual memory may not be similarly affected.[51] There is recent evidence that executive impairments – considered a core feature of progressive VCI – stabilize or improve following stroke,[52] which may in part reflect risk factor management. However, many stroke survivors exhibit cognitive impairments that endure or progress in the years following their incident stroke.

Epidemiology

Demographic and vascular risk factors

Stroke and dementia share several modifiable risk factors, including education and traditional cardiovascular risk factors such as high blood pressure, smoking, and diabetes mellitus (DM).[53,54] However, decades of research have shown that the risk factors for PSCID are more nuanced than those for either stroke or dementia alone.

Older age is associated with faster cognitive decline post-stroke. For example, in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, each one-year increase in baseline age was associated with a 17% higher odds of cognitive impairment per year of follow-up.[55] These findings dovetail with those of non-stroke cohorts, whereby older age is a strong risk factor for the incidence of cognitive impairment.[56] A 2009 synthesis of the available evidence found that stroke survivors with low education were 1.8 times more likely to experience post-stroke dementia.[57] Stroke survivors with high education may be better able to compensate for vascular brain injury, thus maintaining a higher level of function for longer.

The Cognitive Function after Stroke (CogFAST) study reported that the presence of three or more cardiovascular risk factors was associated with a 3.6-fold increase in the risk of post-stroke dementia in an elderly population.[58] With respect to individual vascular risk factors, prevalent DM and atrial fibrillation (AF) have been linked to a higher risk of post-stroke dementia across studies; DM and AF are associated with a 1.5 and 1.9 fold increase in dementia risk, respectively.[57] In addition to contributing to the index stroke, AF has been associated with imaging markers of cerebral small vessel disease (SVD), which in turn may contribute to the risk of cognitive impairment.[59] DM may also exacerbate the overall burden of brain SVD. For instance, a neuropathological analysis of more than 1.300 autopsied patients with DM found that diabetes increased the odds of brain infarcts, particularly lacunes, but not Alzheimer's disease (AD) pathology.[60] As detailed below, the burden of SVD appears to be a key predictor of dementia in stroke patients.

SVD burden can contribute to cognitive impairment and dementia in persons with and without stroke alike.[57,61–63] Since SVD can affect multiple brain regions and show variable involvement of specific white matter tracts, SVD can affect multiple cognitive domains, including executive function, processing speed, and memory.[61,64] Meta-analysis suggests that the presence of leukoaraiosis and atrophy are associated with a 2.3 and 2.2 fold increase in post-stroke dementia risk, respectively.[50,57]

Neuropathologies that are comorbid with cerebrovascular disease likely hasten dementia onset in stroke survivors.[65,66] Persons with mixed neuropathological findings (e.g., SVD and AD) are three times more likely to have dementia than persons with just one neuropathologic diagnosis (e.g., SVD alone).[67] Medial temporal lobe atrophy (a common feature of AD) is a strong risk factor

for post-stroke dementia.[57] Patients with stroke or SVD who have evidence of amyloid-beta (Aβ) deposition experience more rapid cognitive decline than those without Aβ.[68,69] Thus, preclinical AD appears to increase the risk of dementia in stroke patients; further research is needed to investigate other comorbid proteinopathies.

High blood pressure and smoking, while related to both stroke and dementia risk more generally,[53,70] have not been consistently associated with the risk of PSCID.[50,57] Interestingly, the REGARDS study reported that stroke survivors with hypertension, as compared to those without, experienced a slower decline in executive function.[55] Blood pressure is highly dynamic and its relationship with PSCID likely depends on several factors including the timing of measurements relative to the stroke, chronicity of hypertension, and medication use. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) randomized controlled trial showed that antihypertensive therapy reduced the risk of cognitive decline relative to placebo, particularly in participants with recurrent stroke.[71] Although more research is needed, greater blood pressure variability in the early phase post-stroke has been associated with cognitive impairment.[72,73]

As detailed above, several of the known risk factors for post-stroke dementia are potentially modifiable, suggesting that targeted interventions or management plans could reduce the risk of post-stroke dementia. Indeed, the Framingham Heart Study found that the risk of dementia in stroke survivors has been declining over the past three decades.[74] Between 1977 and 1983, the 5-year relative risk of developing dementia was nine times higher in stroke survivors than in individuals free of stroke. Between 2004 and 2008, it was only 40% greater. This risk reduction could in part relate to improved detection of milder strokes. However, improved stroke treatment and management and more successful prevention of secondary ischemic events including recurrent stroke, covert brain infarcts and white matter injury, are also likely contributing factors. These results point towards the importance of refining our understanding of PSCID risk factors and translating those findings into improved outcomes for patients.

Stroke characteristics associated with PSCID risk

Several characteristics of the stroke itself are predictive of post-stroke dementia, including stroke severity and lesion volume. For example, one study indicates that severe stroke advances dementia onset by approximately 25 years, mild stroke advances dementia onset by four years, and TIA by about two years.[50] Two weeks after stroke, lesion volume explains high variance in left motor deficits and language but little variance in verbal and spatial memory.[75] This may be because cognitive functions that are widely distributed throughout cortical regions, such as memory and attention, may be less susceptible focal insults.

There also appears to be an interplay between infarct location and number. Multiple infarcts have long been described as a cause of vascular dementia, often manifesting clinically as a stepwise or fluctuating deterioration in cognitive function.[76] Pooled analysis of the available data also suggests that having multiple strokes leads to a 2.8 fold increased risk of post-stroke dementia.[50,57] With respect to infarct location, left hemisphere strokes confer an increase in risk (OR = 1.4).[57] Since most individuals are left-hemisphere dominant for language and since language underpins performance on many neuropsychological tasks, left-hemisphere stroke may result in cognitive deficits that are more easily detected by formal neuropsychological testing. Furthermore, as language is essential for many activities of daily living and as impairment to activities of daily living is required for a dementia diagnosis, left hemisphere strokes resulting in aphasia may lower the threshold for dementia diagnosis. Even when multiple strokes are present, the spatial distribution of those lesions may be important in causing cognitive impairment. The Age, Gene/Environment Susceptibility (AGES) Reykjavik Study reported that, compared to participants without infarcts, persons with multiple infarcts in the same location did not display poorer memory, processing speed, or executive function.[77] In contrast, multiple infarcts across multiple locations (e.g., cortical and subcortical regions) were associated with poor performance

across all three measured cognitive abilities. Imaging studies have shown that patients with deficits across multiple cognitive domains tend to have damage to so-called 'cross-road' regions where multiple white matter pathways overlap.[75]

Data comparing the risk of PSCID between intracranial hemorrhage and ischemic stroke subtypes have been inconclusive. A 2009 review found that hemorrhagic strokes were not predictive of post-stroke dementia.[57] However, this finding was likely underpowered, with only 15 dementia cases contributing to the pooled effect. A more recent investigation found that, in the population-based Oxford Vascular Study (OXVASC), the risk of post-stroke dementia was 4.5 times higher following hemorrhagic as compared to 2.5 times higher for ischemic stroke.[50] However, this difference in risk was less marked after adjustment for stroke severity and no longer statistically significant after excluding cases with TIA. When comparing data from the general population to data from a Danish medical database comprising 279,349 stroke survivors, the risk of dementia within ten years was 1.6 times higher after ischemic stroke and 2.6 times higher after intracerebral or subarachnoid hemorrhage.[78]

Meta-analysis has identified several stroke complications as predictors of PSCID, including hypoxic-ischemic episodes (odds ratio [OR] = 2.4), incontinence (OR = 3.6), acute confusion (OR = 3.3), dysphasia (OR = 4.1), early seizures (OR = 5.4), recurrent stroke (2.4), and abnormal electroencephalogram findings (OR = 2.7).[57] Complications such as incontinence may be associated with dementia because they exacerbate functional limitations or are associated with greater injury severity or diffuse parenchymal injury.

Genetic contributions to PSCID

Genome-wide association studies (GWAS) as well as studies on familial cases of stroke and dementia have provided major insight into the genetic underpinnings and mechanisms of stroke, SVD, and AD dementia[79]. However, GWAS studies for vascular cognitive impairment are lacking.

Given the huge sample sizes required for GWAS, candidate gene approaches have been used to examine risk factors for vascular dementia and PSCID. A 2015 meta-analysis of genetic polymorphisms for vascular dementia located 69 studies, including 4,462 cases and 11,583 controls.[80] Overall, five polymorphisms were found to associate with vascular dementia, including Apolipoprotein E (APOE) ε4. However, with the exception of APOE ε4, these findings require replication in larger studies.

The APOE ε4 allele is the strongest genetic risk factor for late-onset AD.[81] Moreover, genetic variation in APOE has been associated with SVD markers and cerebral amyloid angiopathy.[82,83] However, the relationship between APOE and dementia risk in stroke survivors has been equivocal.[24] A recent analysis of the Oxford Vascular Study cohort found that ε4 homozygosity was present in 1.7% of stroke survivors. Such individuals displayed a 2.9-fold increase in dementia risk over 5-years (relative to ε3/ε3 carriers).[48] In contrast, ε4 heterozygosity was not associated with an increase in post-stroke dementia risk. Further work is needed to uncover the genetics of PSCID beyond genes related to common brain pathologies in the general population.

Neuropathology

The neuropathological lesion types associated with strokes include large (territorial) infarcts, multiple infarcts, intracerebral hemorrhages, subarachnoid hemorrhages, hemorrhagic infarcts, and secondary brain atrophy after stroke. Besides the impact of lesion type, size, and location itself, there are other neuropathological substrates associated with cognitive decline after stroke that are incompletely understood and appear to be complex. First, there are immediate effects on brain health caused by the tissue changes that arise due to vessel occlusion or vessel rupture. This cascade of events may include excitotoxicity, oxidative stress, blood-brain barrier (BBB)

dysfunction, inflammation, and cell death.[84] In addition, vasogenic edema and hemorrhages may occur in the affected tissue as a result of delayed microvascular damage and BBB leakage.

Besides these direct detrimental effects on the brain parenchyma, it has become increasingly clear that pre-existing structural brain changes, and in particular SVD lesions, are major contributors to the occurrence of cognitive impairment or dementia after stroke.[85] These include changes to the small vessels themselves (*e.g.* arteriolosclerosis and cerebral amyloid angiopathy), as well as their manifestations such as microbleeds, microinfarcts, lacunar infarcts, enlarged perivascular spaces, and white matter lesions (**Figure 2; Table 2**).

Of these, microinfarcts and white matter lesions, typically visible as white matter hyperintensities (WMH) on brain MRI, appear to be the most relevant due to their widespread effects on tissue integrity.[58,86] On neuropathological examination of the brain *post-mortem*, chronic microinfarcts are recognized on standard hematoxylin and eosin sections as focal areas of tissue injury with evidence of cell loss and gliosis, sometimes with cavitation, ranging from 100 µm to a few mm in diameter. Microinfarcts are considered the most abundant form of silent brain infarction and their accrual over time can significantly impact brain structure and function by disrupting connected areas beyond the actual visible lesion boundaries.[87–90]

The neuropathology of WMH is inherently heterogenous and includes white matter rarefaction, ischemia, inflammation, BBB leakage, myelin breakdown, axonal injury, loss of oligodendrocytes, and perivascular space dilation.[91,92] Autopsy studies that directly compared white matter tissue in cases that developed dementia compared to cases that did not develop dementia post-stroke have revealed BBB disruption (*e.g.* loss of pericytes and fibrin extravasation) and irreversible astrocyte injury (in the form of clasmatodendrosis).[86,93] Co-existing neurodegenerative changes such as parenchymal Aβ plaques and neurofibrillary tau tangles have also been implicated.[58,94–96] It is likely that there may be synergistic effects between stroke, small vessel disease, and neurodegenerative pathologies. For example, stroke-induced increases in vascular Aβ accumulation as a result of impaired perivascular Aβ clearance may contribute to the formation of cerebral amyloid angiopathy and dementia.[97,98] Additional studies are needed to further elucidate the neuropathological substrates and pathophysiological mechanisms that are implicated in the development of PSCID.

Pathophysiology

Given the wide range of clinical stroke events, pathophysiology of PSCID varies extensively. All ischemic stroke subtypes (SVD, cardioembolism, large-artery atherosclerosis, or strokes of other determined or undetermined etiology), as well as ICH (lobar or deep) and SAH can cause vascular cognitive impairment or dementia (VCID);[54] consequently, PSCID is recognized as major VCID, along with other traditionally outlined mechanisms including multi-infarct dementia, strategic infarct dementia, subcortical ischemic dementia, "hemorrhagic dementia, and mixed dementia.[33] While mechanistic considerations of interaction between stroke and neurodegenerative pathology apply across the full spectrum of VCID, the underlying disease biology linked to acute stroke insult is still poorly understood. Major knowledge gaps relate to the impact of: (i) specific stroke subtypes and synergistic effects of pre-existing AD or SVD pathology, (ii) stroke lesion characteristics (size, topography, multiple lesions versus single strategic infarct) and post-stroke progression of chronic neurodegeneration and SVD pathology, (iii) the combined effect of patient vascular risk profile, antecedent co-morbidities, and functional baseline, (iv) genetic susceptibility, and (v) acute stroke interventions and post-stroke course on cognitive outcomes.[85,99]

While these questions are being addressed by ongoing large-scale research efforts,[100–103] cognitive dysfunction following an acute stroke event is generally caused by: (a) direct injury to the brain structures critical for cognitive function (e.g., a single “strategic” lesion involving eloquent regions such as thalamus or basal ganglia),[104,105] (b) disruption of the structural and functional connections in the brain (e.g., large lesions, multiple lesions of key brain grey matter structures

or lesions largely impacting white matter),[106–110] and (c) global brain dysfunction due to acute inflammation, neurotoxicity, and metabolic disarray.[111–116] Further, significant variation exists in - inter-individual ability to compensate for both acute injury as well as pre-existing vascular and neurodegenerative burden of disease, a concept known as "brain reserve" or "resilience." Some factors contributing to brain reserve, such as age are also known to affect risk of PSCID (Figure 1), with compensatory mechanisms including vascular remodeling and angiogenesis being possibly attenuated in the aging brain, and resulting in more extensive tissue damage and hence accelerated cognitive decline post-stroke.[84]

At the cellular level, acute stroke related injury ultimately impairs function of the neurovascular unit (NVU), the smallest building block of the brain parenchyma at the center of the vast majority of brain dysfunction.[117–119] The NVU is comprised of multiple cell types including neurons, glia, and vascular cells,[120] which coordinate the unit's critical role in cerebral blood flow regulation and in maintaining intact brain parenchymal milieu, as the BBB's main building block.[121,122] The NVU is commonly implicated in VCID, or mechanisms of mixed dementia,[123] as life-long damage to the cerebral vasculature by untreated hypertension, diabetes or smoking leads to microvascular dysfunction. This in turn causes BBB dysregulation, impaired clearance, and "unauthorized entry" of blood-borne neurotoxic molecules into the brain.[119,124] Reduction of resting cerebral blood flow and accumulation of neurotoxic plasma proteins (fibrinogen, plasminogen, thrombin etc) accelerate neuronal injury and neurodegeneration even in the absence of the known Alzheimer's toxin (Aβ); although, dysregulation of the NVU may accelerate Aβ accumulation through diminished clearance and increased production of Aβ.[125,126] The interaction between these two pathways (Aβ-independent and Aβ-dependent) is considered to be synergistic in contributing to cognitive impairment/dementia.[119,124]

The NVU's ability to withstand cerebrovascular insults, proteinopathy, metabolic disarray, or inflammatory burden is thought to underlie what has recently been termed as "brain health."[124] Conversely, the NVU's failure portends susceptibility to stroke, dementia, or other detectable brain diseases.[123] Given significant overlap between risk factors for stroke, dementia, and PSCID, preserving the NVU integrity through common preventive measures holds promise to promote optimal brain health.[127,128]

Neurocognitive Assessment

Neurocognitive assessment of PSCID is usually motivated by one of two overarching goals, namely either to: 1) screen stroke patients at large for presence of PSCID; or 2) diagnose PSCID in specific individuals, characterize its presentation and follow its evolution over time.[129,130] A number of considerations guiding cognitive testing apply equally to both clinical applications. Reliable diagnosis of PSCID is predicated on application of standardized neuropsychological testing instruments, allowing for both consistent screening practices across stroke patients and meaningful longitudinal follow-up for individuals. Both screening and in-depth examination of cognitive function should capture information on multiple cognitive domains, including at a minimum general orientation, memory, and executive function.[129,130] More in-depth testing aimed at definitive diagnosis and longitudinal follow-up should further capture detailed information on language, and visuospatial processing. **Table 3** shows a practical framework to approach cognitive screening and more in-depth assessment during the natural history of cognitive impairment and recovery following acute stroke. In the hyper-acute setting (Emergency Department and/or Neurocritical Intensive Care Unit) the approach should entirely be focused on PSCID screening.[24] Most experts recommend utilizing tests requiring < 5 minutes for administration, such as the Mini-Cog or abbreviated forms of the MoCA test.[130–132] The National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) previously convened an expert working group and devised recommendations for neurocognitive assessment standards in the diagnosis and study of VCID.[129] Based on available evidence we

recommend using the NINDS-CSN 5-minute protocol including the Orientation, Memory and Phonemic fluency MoCA subtests for PSCID screening in the acute setting.[129,133,134] Of note, the brief screening tests advocated above have proven validity in assessment of older adults, but current evidence for their use in PSCID screening is far more limited.[130]

In the hyperacute setting it is further advocated to screen for delirium, which affects 25 to 40% of patients during the acute period, and has implications for longer term cognitive outcomes.[135] The Confusion Assessment (CAM) has proven accuracy for diagnosis of delirium after stroke, and a modified version for intensive care unit use (CAM-ICU) incorporates picture-based, non-verbal responses to aid in assessment of patients with aphasia or other language disorders.[136,137] Upon the patient having achieved medical stabilization more in-depth assessment for cognitive performance can be pursued, usually in a stroke unit setting. In these instances, administering a detailed, full neuropsychological testing battery is generally unfeasible. Experts therefore recommend utilizing a validated global cognition screening test, with preference (based on currently available evidence) given to the MoCA or Oxford Cognitive Screen (OCS). The MoCA has the largest body of literature supporting its use, although the validated cut-off (< 26) has shown to have very high sensitivity and specificity for PSCID.[138,139] The OCS, however, does offer some advantages, such as domain-specific results and finger-pointing response to aphasia-related testing bias.[140] Stroke survivors screening positive in the hyperacute and acute settings should be administered a detailed neuropsychological testing battery in the subacute setting (ideally within the first 90 days of stroke), usually in a dedicated rehabilitation facility or at outpatient stroke neurology follow-up.[24] The NINDS-CSN working group generated recommendations for two detailed neuropsychological testing protocols lasting 60 and 30 minutes, respectively, that can be readily applied to assessment of PSCID (**Table 4**).[129] These batteries include tests with population normative data, validated versions in several languages, and can also be utilized for longer-term clinical and research purposes in the months and years following acute stroke.[141,142] While screening for pre-stroke cognitive impairment is rarely feasible in the hyperacute and acute settings, in-depth evaluation of PSCID in the subacute setting should include assessment for premorbid cognitive performance to inform the diagnostic process. This is best achieved by use of informant standardized questionnaires, with different versions of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) being used extensively in both clinical and research settings.

Neuroimaging

Neuroimaging is a key research tool in PSCID with increasing value for clinical application. Imaging offers mechanistic insight into pathophysiology and adds to prediction models of outcome. While computed tomography is widely available and can be applied to approximate parameters of clinical relevance, such as infarct volume, brain volume, pre-existing infarcts and severity of leukoaraiosis,[143] MRI is the most informative method and thus the main focus of this section.

An emerging theme in longitudinal imaging studies of stroke survivors is secondary neurodegeneration, i.e. neurodegeneration in remote brain regions distant from the infarct (**Figure 3A**).[144] Selective cortical thinning was found six months post-stroke in regions connected to subcortical infarcts.[145,146] Increased iron deposition in the ipsilateral thalamus after non-thalamic stroke likewise suggests remote degeneration.[147] MR imaging studies have further shown widespread white matter changes six months post-stroke in the ipsilateral hemisphere, which were found to correlate with circulating levels of serum neurofilament light chain (NfL), providing biomarker evidence for neuroaxonal degeneration.[148] Functional and structural brain network studies complement the effort to understand these wide-spread effects after stroke,[149,150] and can unravel compensatory and recovery mechanisms.[151]

There are multiple parameters from baseline MRI with predictive value for cognitive outcome after stroke, the most consistent factor being brain atrophy.[99] A recent, large collaborative study on almost 3000 stroke survivors systematically assessed the effect of infarct location on PSCID using voxel-based lesion-symptom mapping.[105] This study found infarcts in the left frontotemporal lobes, left thalamus, and right parietal lobe to be strongly associated with PSCI and provided maps assigning infarcts to PSCID risk strata based on anatomical location.[105] These maps are available for public access (https://metavcimap.org/features/software-tools/location-impact-score/) and serve as an example of research findings translating into clinical applications.

Identification and precise quantification of pre-existing comorbid diseases may aid the prediction of PSCI and inform on underlying mechanism. Among the most relevant factors in stroke patients is cerebral SVD (see section on neuropathology above). Aside from being a major cause of stroke, SVD has been recognized as one of the most frequent comorbidities in patients with other stroke etiologies (**Figure 3B**). A recent meta-analysis has highlighted the association between WMH, a hallmark of SVD on MRI, and PSCID as well as other long-term outcomes.[152] WMH can be assessed quantitatively by lesion segmentation or semi-quantitatively by rating scales that can be used routinely in clinical practice. The impact of other MRI manifestations of SVD,[153] such as cerebral microbleeds,[154] on stroke outcome is currently being investigated. Also, there is increasing recognition of diffusion MRI markers as precise and reliable metrics of SVD burden.[155,156]

The role of pre-existing AD pathology in PSCID remains controversial. Studies using the AD imaging hallmarks medial temporal lobe and hippocampal atrophy as potential predictors of PSCID have been inconclusive.[57] Notably, hippocampal atrophy might also be driven by other factors, such as SVD.[157] Also, imaging studies combining positron emission tomography (PET) with tracers directed at Aβ did not find amyloid pathology to be a key factor for the development of PSCID.[158,159]

Fluid Biomarkers

Emerging data suggest that important markers of PSCID may be found in the peripheral blood. Though precise indicators of PSCID likely mandate incorporation of the affected regions and pathways in the brain provided by imaging techniques, fluid biomarkers can provide a rapid, easily accessible, and potentially valuable tool that may function as both risk *and* prognostic biomarkers.[160] Varying post-stroke injury cascades may influence the development of PSCID including inflammation, neuro-axonal injury, vascular injury, and the activation of neurodegenerative pathways.[85] Recent reports indicate that windows into each of these processes are available in peripheral blood.

Neuro-axonal injury, as measured by circulating levels of NfL, provide the most robust measure that is likely to be associated with PSCID. Blood NfL levels rise rapidly in the days and weeks after acute stroke and several studies associate blood Nfl levels with prognosis as measured by the modified Rankin Scale[148,161–164] Separately, blood NfL levels are associated with AD and cognitive impairment from cerebral SVD.[165–168] As PSCID is in part driven by the extent of axonal injury resulting from stroke, layered upon any pre-existing neuro-axonal injury, circulating NfL levels are poised to achieve a role in evaluating risk of PSCID and establishing prognostic expectations of cognitive impairment after stroke.

Beyond the structural injury to the brain caused by stroke, PSCID is likely to be accelerated by pathways implicated in neurodegeneration including Aβ and tau accumulation. Low Aβ ratios (42:40) and plasma total tau have both been shown to be predictive of future cognitive decline

and post-mortem evidence of AD pathology in otherwise cognitively intact individuals.[169–173] Post-translational modifications of tau, specifically phosphorylation events that are thought to promote its accumulation into neurofibrillary tangles are activated by stroke[174] and of particularly high sensitivity in detecting Alzheimer's pathology.[175] Plasma phospho-tau 181 and phospho-tau 217 detect clinical AD with high sensitivity and thus deserve to be explored as risk biomarkers for PSCID.[176–178]

At its core, stroke is fundamentally a vascular injury and as such, indirect measures of impaired BBB permeability such as fibrinogen levels and aquaporin-4 have also been implicated in PSCID.[179–181] Similarly, changes in angiogenic signaling have been implicated in the aging process[182] and can be easily measured in blood. Elevations of circulating levels of angiogenic signaling molecules may implicate a failure of angiogenesis and poor collateral blood flow pathways in individuals at risk for PSCID.[183]

Finally, inflammation is a well-recognized cause and consequence of stroke and likely contributes to PSCID in selected individuals by synergizing with baseline levels of inflammation measurable in plasma that are known to associate with cerebral SVD.[114,184] Thus, numerous fluid biomarkers are likely to emerge as reliable risk and prognostic tools for PSCID serving to augment clinical and imaging-based assessments.

Management

Prevention

Despite strong epidemiological foundation for a role of vascular risk factors in cognitive decline and dementia,[127,185–187] there is limited evidence from randomized controlled trials (RCTs) that controlling vascular risk factors through interventions would lower the risk of incident PSCID.[23,185]

Few RCTs have examined the effects of intensive blood pressure (BP) management on cognitive decline and incident dementia in patients with a antecedent stroke: the Nimodipine In preventing Cognitive impairment in ischemic cerebrovascular Events (NICE),[188] Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS),[189] and Secondary Prevention of SubCortical Stroke Study (SPS3)[190] trials included patients with a recent IS (maximum interval from stroke onset: 90 days), whereas the PROGRESS trial [191] included patients with either IS or HS within an interval up to 5 years from stroke onset. Compared to placebo, BP lowering therapy had no effect on dementia incidence (two trials) and incident mild cognitive impairment (one trial). In NICE and PROGRESS, there was a modest effect of BP lowering therapy on the prevention of cognitive decline as defined by a ≥3-point drop in the Mini-Mental State Exam (MMSE) score. Overall, however, the quality of evidence is insufficient to recommend intensive BP lowering solely for the prevention of PSCID.[23] The same applies to statin treatment,[23] for which there is limited information from the Japan Statin Treatment Against Recurrent Stroke (J-STAR) trial.[192]

Current guidelines recommend against the use of dual antiplatelet therapy compared to single antiplatelet therapy for the prevention of cognitive decline or dementia following lacunar infarction.[23] The recommendation is based on results from SPS3, which found short-term dual antiplatelet treatment (aspirin 325 mg plus clopidogrel 75 mg vs. aspirin 325 mg plus placebo) to have no beneficial effect on mild cognitive impairment incidence or cognitive decline, while being associated with an increased risk of bleeding.

Observational studies suggest life style factors as a target for dementia prevention but there is insufficient evidence from RCTs to recommend monitored lifestyle interventions solely for the prevention of PSCID.[23] The Austrian Polyintervention Study to Prevent Cognitive Decline after

Ischemic Stroke (ASPIS) trial examined the effects of a multidomain intervention that simultaneously targeted BP, lipid and glycemic control, healthy diet, physical activity, and cognitive training.[193] Another trial compared an intervention that combined advice on risk factor management with smoking cessation courses, physical activity, and healthy diet with usual care.[194] Both trials recruited patients shortly after stroke but neither of them found a significant effect on cognitive outcomes. The effects of physical activity on cognitive decline post-stroke were investigated in the Life After Stroke Trial (LAST)[195] and MoveIT trial,[196] but again, there was no clear effect on cognitive outcomes.

Overweight and obesity states are established risk factors for cognitive decline and dementia. Yet, disentangling the influence of obesity from the influence of insulin resistance and other components of the metabolic syndrome on cognitive decline remains challenging and there are no interventional studies that have examined the effect of weight reduction on the risk of cognitive decline. While low educational level is associated with an increased risk of cognitive impairment and dementia including in patients with a history of stroke,[23,57] there is uncertainty over the benefits of structured cognitive training as a single intervention for the prevention of cognitive decline and dementia after stroke.[23] Overall, there is a lack of methodologically robust and adequately powered studies in this area.

Some investigators have advocated the use of animal-derived nootropics for the prevention of VCID. There was a small (N=503 patients) RCT in IS patients and a MoCA ≤25, who were randomized within 1-week post-stroke to receive actovegin, a deproteinized hemoderivative of calf blood, or placebo for 6 months followed by 6 months of standard therapy. Treatment with actovegin was found to be associated with significant improvements on the ADAS-cog when compared to placebo.[197] However, the effect size was small and there are some safety concerns causing uncertainty over the benefits and risks of actovegin.[23]

Given the well-documented association between stroke, in particular severe stroke, and risk of dementia and an even higher risk of dementia in those with recurrent stroke,[50,57] there is strong reason to believe that treatments with proven efficacy for stroke prevention will also prevent cognitive decline.[198] In light of this and the above data, the American Heart Association / American Stroke Association provided specific recommendations on risk factor management[40,127] and recommends checking health status with "*Life's Simple 7*" (nonsmoking, physical activity at goal levels, healthy diet consistent with current guideline levels, body mass index <25 kg/m2, blood pressure <120/<80 mm Hg, total cholesterol <200 mg/dL, and fasting blood glucose <100 mg/dL) to maintain optimal brain health.[127]

Symptomatic Treatment

Currently, there is no pharmacological treatment approved for PSCID. There have been several trials of cholinesterase inhibitors (galantamine, donepezil, or rivastigmine) in patients with vascular dementia,[199–201] but only one trial with a focus on PSCID.[202] This trial randomized 50 patients, who had PSCI/no dementia at 3 months post-stroke to either rivastigmine or placebo. Within a treatment duration of 24 weeks there was no benefit across the primary (executive function) and secondary outcomes (global cognitive function, activities of daily living, behavioral and psychological symptoms). A network meta-analysis of trials using cholinesterase inhibitors in patients with vascular dementia and other VCI found some evidence that donepezil and galantamine may improve cognition but concluded that this effect is unlikely to be clinically important.[200] Memantine is a glutamate NMDA (N-Methyl-D- aspartate) receptor antagonist that has been approved for symptomatic treatment in moderate to severe dementia due to AD. As for cholinesterase inhibitors there is no evidence to suggest a clinically relevant benefit of treatment with memantine in patients with vascular dementia.[203] Yet, many elderly patients with stroke have neurodegenerative disease that may benefit from treatment with cholinesterase inhibitors or

memantine and stroke should not be a barrier to considering treatment with these agents if there is a suspicion of concomitant AD.[23,204]

Cognitive rehabilitation, in particular interventions based on re-learning of compensatory strategies have shown promise in small interventional studies.[23,204] However, there is continued uncertainty on the benefits of cognitive rehabilitation interventions due to a lack of methodologically robust trials.[23] There is some evidence that noninvasive brain stimulation might transiently improve cognitive function post-stroke but additional data from sufficiently powered trials are needed to fully assess this therapeutic modality (PMID: 35109684). As an important aspect, treatment plans in PSCID should address comorbidities, such as behavioral and psychological symptoms, support for patients and caregivers, and maximizing independence.[23,33,204]

Future Directions

While substantial progress has been made in conceptualizing VCID ,[33,123] the precise mechanisms of PSCID are insufficiently understood.[99,205] The hypothesis that a specific stroke event may precipitate, accelerate, or unmask cascades of neurodegeneration and microvascular dysfunction in a vulnerable brain requires rigorous investigation. Further, the recently proposed construct of ”brain health” purports protective factors that constitute brain’s ability to withstand the effects of acute insult or allow the brain to recover fully and rapidly to its pre-stroke level of function, i.e. mechanisms of brain resilience in stroke.[34,119,127]

Considering the complexity of underlying disease processes in PSCID, there is an urgent need for a coordinated, global research effort to close the existing knowledge gaps in this field.[85] A number of large-scale international research consortia focus on understanding VCID etiology and developing treatable targets to lessen the burden of VCID worldwide including DEMDAS (The Determinants of Dementia after Stroke Study),[101] STROKOG (Stroke and Cognition Consortium),[100] SVDs@target (Small Vessel Diseases-at-target), HBC (The Heart-Brain Connection), MarkVCID,[102], the ISGC (International Stroke Genetics Consortium), and a Network on “Understanding the Role of the Perivascular Space in cerebral SVD”.[26] More recently, DISCOVERY (*Determinants of Stroke Cognitive Outcomes and Vascular Effects on Recovery*), a prospective, multi-center observational cohort study aiming to enrol 8,000 non-demented racially/ethnically diverse patients with incident IS, ICH and SAH admitted across 30 high-volume US stroke centers has been funded by the National Institutes of Health (www.discoverystudy.org). DISCOVERY participants are followed for a minimum of 2 years with serial in-person and phone-based cognitive and functional assessments, and with subgroups of participants undergoing detailed MR and PET imaging as well as blood collection for plasma biomarkers, genome sequencing, epigenetics, and gene expression studies.[85] DISCOVERY aims to understand cognitive decline and dementia in high-risk US populations based on their stroke events type or the underlying vulnerability to PSCID. Utilizing this knowledge and the findings from the multiple ongoing international research studies in VCID, the global community must forge the future of personalized post-stroke interventions to reduce overall burden of PSCID and related disability. *Furthermore, we propose to consider cognitive outcomes after stroke using harmonized timing and methods of assessments for patients of all stroke subtypes (IS, ICH, and SAH) as the new standard for all clinical trials of post-stroke outcomes.*

As population ages globally, brain health is becoming one of the most important concepts to embrace as part of the public health priorities in order to optimize quality of life and to control health care costs worldwide.[206] Brain health implies optimal function and freedom from neurological injury, which is intimately connected to prevention of PSCID. While no personalized prediction of trajectories of cognitive impairment after stroke is currently available, there is growing interest in PSCID, and its prevention, given the changing epidemiology of post-stroke survivors -

with older individuals surviving longer. Reducing the incidence of dementia by preventing stroke,[198] modifying the overall burden of cerebrovascular and cardiovascular disease, and though that, augmenting individual brain reserve and resilience[34] throughout life-course of individuals and communities is key to attaining population brain health. Therefore, the next step is to incorporate the mechanistic insights from the ongoing research efforts in PSCID and to develop personalized approach to diagnosis, management, and prevention of cognitive impairment and dementia after stroke, and though that, explore the new frontiers in brain health.

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Table 1. Stroke characteristics, risk factors for and rates of PSCID. *Shown is a selection of recent studies reporting rates of post-stroke cognitive impairment/dementia diagnosis in patients with variable stroke subtypes without pre-stroke dementia and an ascertained stroke event.*

	PSCID rate	Timing of diagnosis post-stroke	Stroke subtype	Risk factors		
				Stroke characteristics	Clinical	Radiographic
Pendlebury et al. (2009)[57]	12-20.3%* (hospital based) 7.4% (population-based)	Variable	IS, HS	HS, left hemisphere, stroke severity, prior stroke, multiple strokes, recurrent stroke, dysphasia	Older age, lower education level, prior cognitive decline, functional disability, DM, AF	Leukoaraiosis, atrophy, infarct volume, MTLA
Wong et al. (2012)[207]	73%	3 months	SAH	Aneurysmal SAH	NA	Delayed cerebral infarction
Douiri et al. (2013)[208]	24%	3 months	IS, ICH, SAH	Anterior circulation infarct	Older age, Black race, SES	Lacunar infarcts, large-artery atherosclerosis
Mok et al. (2016)[209]	4.4%	3 years	IS, TIA	NA	Older age, HTN, DM	Multiple lacunar infarcts, WMH
Moulin et al. (2016)[19]	14.2%	1 year	ICH	Lobar location	Older age	Superficial siderosis, cortical atrophy, higher CMB count
Biffi et al. (2016)[210]	19%	6 months	ICH	Lobar location	Older age, APOE e2 variant	Hematoma volume
Arba et al. (2017)[211]	34%	1 year	IS, HS, TIA	Stroke severity	Older age, HTN, DM, leg paralysis	NA
Pendlebury et al. (2019)[50]	34.4% (NIHSS>10) 8.2% (NIHSS <3) 5.2% (TIA)	1 year	IS, ICH, TIA	Stroke severity, prior stroke	Age, previous stroke, dysphasia, baseline cognition, low education, pre-morbid dependency, DM	Leukoaraiosis
Lo et al. (2019)[9]	44% (global)	2-6 months	IS, HS, TIA	Prior stroke	HTN, DM, AF, CHF	NA

Koton et al.(2022)[10]	23.3%	≥ 1 year	IS	Stroke severity, number of recurrent strokes	Systolic BP, HTN medication use	NA

** first-ever or recurrent stroke included*

Abbreviations: AF – atrial fibrillation, APOE -apolipoprotein E, BP – blood pressure, CHF – congestive heart failure, DM – diabetes mellitus, ICH – intracerebral hemorrhage, IS – ischemic stroke, HTN – hypertension, HS – hemorrhagic stroke, MTLA – medial temporal lobe atrophy, NIHSS – National Institutes of Health Stroke Scale score, PSCID – post-stroke cognitive impairment/dementia, SAH – subarachnoid hemorrhage, SES – socioeconomic status, TIA – transient ischemic attack, WMH – white matter hyperintensities.

Table 2. Neuropathological characteristics of pre-existing small vessel disease changes contributing to post-stroke cognitive impairment/dementia.

Lesion	Neuropathological characteristics
Arteriolosclerosis	Hyaline thickening of arterioles, loss of vascular smooth muscle cells, and luminal narrowing
Cerebral amyloid angiopathy	Deposition of amyloid β in the walls of leptomeningeal arteries, cortical arterioles, and capillaries, loss of vascular smooth muscle cells
Microbleeds	Acute phase: extravascular intact or lysed erythrocytes / Subacute phase: blood-breakdown products including biliverdin, hematoidin, and hemosiderin / Chronic phase: iron-positive hemosiderin-laden macrophages
Microinfarcts	Acute phase: tissue pallor with hypoxic (*i.e.* eosinophilic or 'red') neurons / Subacute phase: macrophages, reactive astrocytes / Chronic phase: tissue "puckering" or cavitation with a rim of reactive fibrillary astrocytes
Lacunar infarcts	Tissue cavitation with evidence of neuroinflammation in the form of macrophages and peri-lesional reactive astrocytes
Enlarged perivascular spaces	Fluid and extracellular matrix-filled dilated peri-arteriolar spaces
White matter injury	Rarefaction of the white matter, loss of myelin, axonal injury, oligodendrocyte loss, reactive astrocytes, macrophages, dilated perivascular spaces, blood-brain barrier leakage, neuroinflammation

Table 3. Proposed Framework for Neurocognitive Assessment of PSCID.

Time from Stroke Onset	**Acute Stroke Care (Onset to 7 days)***	**8-90 Days**	**3-12 Months**	**1 Year and Beyond**
Setting	ED / ICU / Stroke Unit	Rehabilitation Facility Stroke Clinic	Primary Care Stroke Clinic	Primary Care Neurocognitive Clinic
Assessment Approach	Screening Only	Diagnosis (if positive prior screening) *versus* ongoing screening		
- Screening Test	Yes	Yes	Based on clinic context	
- In-depth Testing	No	If positive prior screening (or research purposes)		
- Delirium Screening	Yes	Based on clinic context		

* based on individual patients' clinical context and local practice patterns, the acute stroke care phase may be considered completed before 7 days or last considerably longer.

Abbreviations: ED – Emergency Department, ICU – Intensive Care Unit, PSCID – post-stroke cognitive impairment/dementia

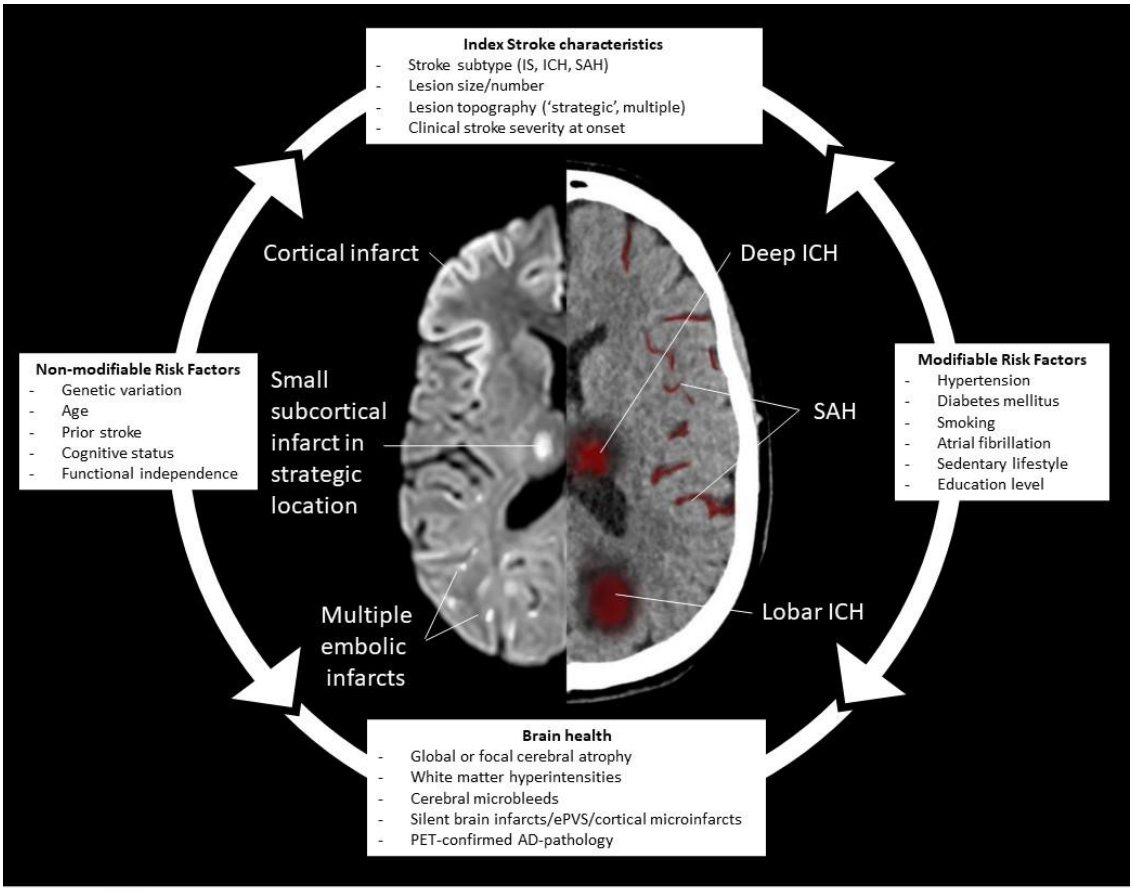
Table 4. NINDS-CSN Neuropsychological Testing Batteries for PSCID.*

60-minute Protocol	
Domain	**Test**
Global	Mini-Mental State Examination (MMSE)
Orientation	MoCA 6-item orientation
Executive	Semantic Fluency (Animal Naming)
	Phonemic Fluency (Controlled Oral Word Association)
	WAIS-III Digit Symbol Coding
	Trail Making Test (A and B)
Visuospatial	Clock Drawing
	Rey-Osterrieth Figure
Language	Boston Naming Test, Short Form
Memory	Hopkins Verbal Learning Test; Revised (HVLT-R)
Depression	Center for Epidemiological; Studies-Depression Scale (CESD)
Apathy	Apathy Evaluation Scale (AES)
Other Neuropsychiatric	Neuropsychiatric Inventory, Questionnaire Version (NPI-Q)
30-Minute Protocol	
Domain	**Test**
Global	Mini-Mental State Examination (MMSE)
Orientation	MoCA 6-item orientation
Executive	Animal Naming
	Controlled Oral Word Association
	WAIS-III Digit Symbol-Coding
Memory	HVLT-R
Depression	CES-D-10
Other Neuropsychiatric	NPI-Q

Adapted from Hachinski, V. et al. National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards. Stroke **37, 2220–2241 (2006).*

Abbreviations: CSN – Canadian Stroke Network, NINDS - National Institute of Neurological Disorders and Stroke, PSCID – post-stroke cognitive impairment/dementia

Figure 1. Risk factors and trajectories of post-stroke cognitive impairment/dementia. A variety of acute ischemic or hemorrhagic insults to a brain with pre-existing microvascular or neurodegenerative disease can initiate a series of pathological events leading to variable trajectories of cognitive decline. Both the risk and temporal trajectories of PSCID are determined by a complex interplay of multiple factors including modifiable and non-modifiable risk factors, index stroke characteristics, and the overall brain health.



** Level of cognitive function at the time of stroke. Note that some individuals experience cognitive decline prior to stroke.*

Abbreviations: AD – Alzheimer's disease, ePVS – enlarged perivascular spaces, ICH – intracerebral hemorrhage, IS – ischemic stroke, PET – positron emission tomography, SAH – subarachnoid hemorrhage

Figure 2. Neuropathological substrates of small vessel disease.

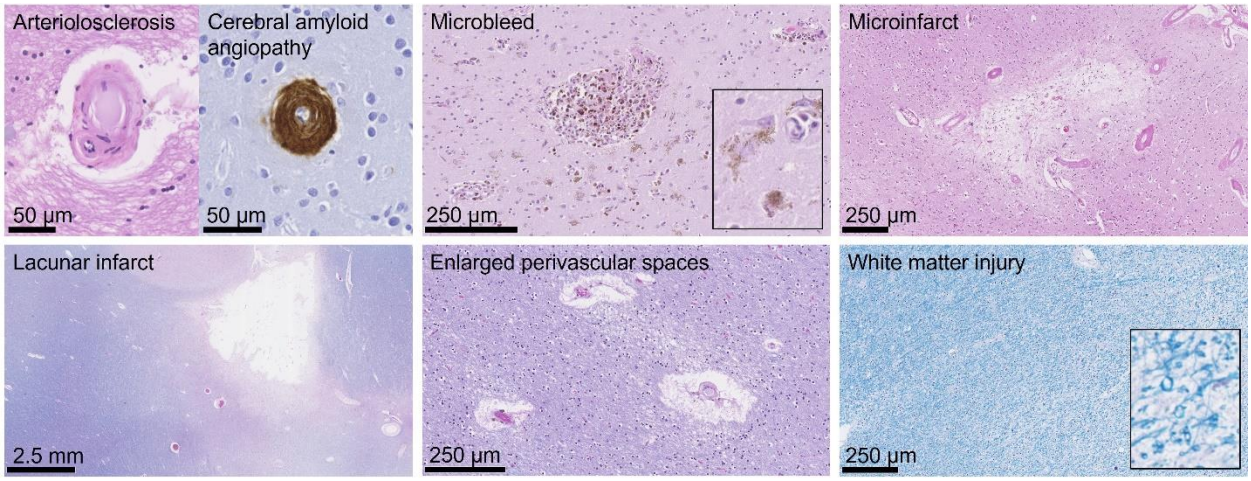


Figure 3. Advanced MR imaging and circulating biomarkers facilitate understanding of PSCID mechanisms. *Panel A*: neuroimaging changes indicative of remote, secondary degeneration after stroke and links to elevated serum neurofilament light chain levels in the (sub)acute and chronic phase. *Panel B*: embolic stroke (red) in a patient with atrial fibrillation and comorbid cerebral small vessel disease (blue).