Section A -Research paper

Post Ischemic Stroke Cognitive Impairment: Prevalence, Diagnosis and Treatment

Khaled Aly El-Sharkawy, Iman Mosbah Abdelgawad Abdelhalim, Takwa Hoseiny Mohamed, Rania Yehia Helal

Neurology Department, Faculty of Medicine, Zagazig University

Corresponding author: Iman Mosbah Abdelgawad

Email: imanmosbah0@gmail.com, **Mobile:** 01024404823

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Abstract:

Stroke, characterized as a neurological deficit of cerebrovascular cause, is very common in older adults. Increasing evidence suggests stroke contributes to the risk and severity of cognitive impairment. People with cognitive impairment following stroke often face with quality-of-life issues and require ongoing support, which have a profound effect on caregivers and society. The high morbidity of post-stroke cognitive impairment (PSCI) demands effective management strategies, in which preventive strategies are more appealing, especially those targeting towards modifiable risk factors.

Keywords: stroke**,** PSCI, cognitive.

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Introduction:

Post-stroke cognitive impairment (PSCI) is one of the major complications after a stroke and is a subtype of vascular cognitive impairment **(1)**. It has been reported that stroke increases the risk of cognitive impairment by at least five to eight times ***(2).***

It ranges in severity from mild to severe and occurs in up to 60% of stroke survivors in the first year after stroke, with a higher rate seen shortly after stroke **(3).**

Up to 20% of individuals with mild PSCI recover fully, with the highest rate of recovery seen shortly after stroke. However, improvement in cognitive impairment without return to pre stroke levels is more frequent than complete recovery **(4).**

Definitions

PSCI is defined as failure in any cognitive domain after stroke: executive function; memory; language; visuospatial ability; or global cognitive function. Poststroke dementia (PSD) is defined as any dementia occurring after stroke: vascular dementia; Alzheimer's disease or other degenerative dementia; or mixed dementia. The concepts PSCI and PSD usually refer to conditions occurring after symptomatic strokes with corresponding ischemic findings upon neuroradiological imaging. Also, seemingly asymptomatic strokes – a common incidental finding in patients both with and without symptomatic strokes – add to the vascular burden of the brain ***(5).***

The following are key definitions differentiating vascular cognitive impairment (VCI) and dementia from PSCI and dementia: VCI refers to cognitive impairment of any severity associated with cerebrovascular disease regardless of the occurrence of stroke symptoms **(6).**

The types of vascular injuries leading to VCI range from an insidious, progressive accumulation of microvascular pathological changes (e g, diffuse white matter injury detected on magnetic resonance neuroimaging as white matter hyperintensities or leukoaraiosis, cerebral microbleeds, enlarged perivascular spaces, or cortical microinfarcts) to a single or multiple clinical stroke events affecting brain structures critical for cognition. Vascular dementia is the end of a continuum of severity of clinical manifestations of VCI **(4).**

PSCI refers to any severity of cognitive impairment, regardless of cause, noted after an overt stroke**.** Poststroke dementia (PSD) is the end of a continuum of severity of clinical manifestations of PSCI and refers to all types of dementia after stroke **(4).**

Prevalence and Incidence Of PSCI

The prevalence of cognitive impairment after ischemic stroke differs by the timing of assessment, diagnostic criteria, demographics (e g, age, race, or ethnicity), era of study publication, and case mix (e g, stroke severity, prior/recurrent stroke, pre stroke dementia, population versus hospital based, interval from stroke, inclusion of patients with aphasia), resulting in substantial heterogeneity in reported estimates **(7).**

PSCI is most common in the first year after stroke, occurring in up to 60% (cumulative incidence) of stroke survivors, with the highest rate seen shortly after stroke. About 44% of individuals are impaired in global cognition 2 to 6 months after stroke **(3)** However, a large population of stroke survivors have cognitive impairment that is not sufficient to meet diagnostic criteria for dementia but still affects quality of life **(8).**

cohort of individuals with mild stroke that excluded pre stroke cognitive impairment, the overall frequency of 3-month PSCI was 47.3% **(9)** the prevalence of PSD varies by stroke severity and history of stroke recurrence, and PSD occurs less frequently than milder forms of cognitive impairment (**10).**

Racial differences in the frequency and severity of PSCI have been reported **(11)** Stroke in Black patients results in a greater cognitive decline and is more frequently associated with dementia within 5 years of ischemic stroke compared with White patients, despite Black patients being younger at the time of the incident stroke **(12).**

Pathophysiology of PSCI

In the general population, small-vessel disease is the biggest contributor to VCI and dementia, whereas in the poststroke population, there is a relatively greater contribution from larger, more destructive embolic infarcts. The exact pathophysiology of PSCI is not well understood given the paucity of knowledge about the effects of specific stroke subtype (acute ischemia, ICH, or aneurysmal SAH), as well as the variable contributions of the severity of the injury, the lesion location, and the interaction between the preexisting brain pathology and an acute stroke event, which may serve as a trigger for or accelerate cognitive decline in a vulnerable brain **(13).**

In most brains affected by stroke, there are diffuse age-related changes involving the smallest building block of the brain parenchyma, the neurovascular unit, which includes neurons, astrocytes, pericytes, microglia, and blood vessels **(14).**

The neurovascular unit is the key structural element of what has been called brain health, or the capacity of the brain to operate at its optimal state of structural and functional integrity, in the absence of or despite the impact of insidious or precipitous injuries related to cerebrovascular dysfunction, metabolic disarray, proteinopathies, or inflammatory responses **(15).**

The structural elements of the neurovascular unit are often damaged by stroke-related injury, possibly leading to PSCI **(16)** However, the same elements can also be considered points of intervention for future treatments, rehabilitation, and prevention strategies involving lifetime environmental exposures, vascular risk factor modification, and even gene therapies **(17).**

Risk factors of PSCI

Risk factors for PSCI reflect pre stroke cognitive decline, preexisting cerebral vulnerability/reduced reserve, and the impact of the stroke; a minor stroke may precipitate dementia in an older person with a vulnerable brain **(18)** key vulnerability factors include age,

cerebral small-vessel disease, and neurodegeneration, which may be partially mitigated by higher educational attainment and premorbid intelligence (indicators of cerebral reserve) **(19).**

Comorbid poststroke depression is also an important factor associated with PSCI, and the two disorders frequently coexist, possibly through shared mechanisms. The risk associated with the effects of late-life vascular factors on early poststroke cognitive decline is unclear except for diabetes, which has been associated with an increased risk **(3)** strong social networks may be a protective factor, although evidence specifically in PSCI is sparse.

PSCI is more common with higher stroke lesion load such as in severe or recurrent strokes **(17)** the risk of PSCI varies with stroke subtype (higher in hemorrhagic and cardioembolic stroke compared with lacunar stroke), likely driven partially by the corresponding stroke severity. Lesion location is important because risks are higher in stroke affecting specific brain regions **(20).**

Brain imaging findings (lesion volume, white matter hyperintensities, atrophy) are proxies for stroke severity and brain vulnerability, with lobar microbleeds and global small-vessel disease burden being important predictors of dementia after stroke. However, it remains unclear to what extent imaging biomarkers predict PSCI over and above clinical factors, including acute cognitive status (delirium, low cognitive test score), which is a powerful predictor capturing both pre stroke decline and lesion impact **(21).**

Poststroke delirium is associated with higher risk for PSD and lower survival. *APOE* ε4 homozygous genotype is a possible risk factor for pre stroke dementia and PSD, accelerating early decline after major stroke and increasing the probability of later dementia after less severe events **(22).**

Knowledge gaps remain, particularly in our understanding of the role of noncerebral factors, including infection, frailty, and social factors. Further studies are needed to understand the independent predictors of poststroke cognitive decline and whether blood and cerebrospinal fluid biomarkers and brain imaging add predictive value over clinical factors **(23).**

Screening and Diagnostic Modalities

Anosognosia, or lack of awareness of the presence or severity of a person's own cognitive deficits, often results in underreporting of cognitive problems. Additional information can be gathered from collateral sources such as family members or caregivers. Informant report is specific but insensitive to PSCI and can be affected by interpersonal and cultural factors **(24).**

Thus, although the report of cognitive decline by patients and their informants is important, objective cognitive assessment is crucial to accurately identify cognitive dysfunction, particularly when anosognosia is present. Although there is no gold standard for cognitive screening after

stroke, several brief cognitive screening tests (≤30 minutes) have been used to identify PSCI. The Mini-Mental State Examination and the Montreal Cognitive Assessment have been the most widely studied cognitive screening instruments **(25)** with the Montreal Cognitive Assessment generally being recommended over the Mini-Mental State Examination **(26)** particularly in subacute phases after stroke (**27)** because it has less of a ceiling effect and is more sensitive to mild cognitive impairment. However, several other cognitive screens show initial evidence for their utility in identifying cognitive impairment after stroke **(25).**

According to the validation study, the sensitivity and specificity of the MoCA for detecting MCI were 90% and 87% respectively, compared with 18% and 100% respectively for the MMSE. Subsequent studies in other settings were less promising, though generally superior to the MMSE **(28).**

Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a widely used screening assessment for detecting cognitive impairment It was created in 1996 by Ziad Nasreddine in Montreal, Quebec. It was validated in the setting of mild cognitive impairment (MCI), and has subsequently been adopted in numerous other clinical settings. This test consists of 30 points and takes 10 minutes for the individual to complete. The original English version is performed in seven steps, which may change in some countries dependent on education and culture. The basics of this test include short-term memory, executive function, attention, focus, and more **(29)** .

Format of Montreal Cognitive Assessment

The MoCA is a one-page 30-point test administered in approximately 10 minutes. The test and administration instructions are available for clinicians online. The test is available in 46 languages and dialects include Arabic **(30).**

The MoCA assesses several cognitive domains:

- The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately five minutes.
- Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point).
- Multiple aspects of executive function are assessed using an alternation task adapted from the trail-making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points).

- Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each).
- Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task.
- Abstract reasoning is assessed using a describe-the-similarity task with 2 points being available.
- Finally, orientation to time and place is evaluated by asking the subject for the date and the city in which the test is occurring (6 points).

- In this clock drawing task, the subject is asked to draw a clock with the hours and showing the time 2:30. Successive results show a deterioration of pattern processing ability in a subject as they progress from mild cognitive impairment (MCI) to severe Alzheimer's disease (AD).

Other applications of MoCA

Since the MoCA assesses multiple cognitive domains, it can be a useful cognitive screening tool for several neurological diseases that affect younger populations, such as Parkinson's disease**(31**) vascular cognitive impairment Huntington's disease, brain metastasis, sleep behaviour disorder primary brain tumors (including high and low grade gliomas), multiple sclerosis and other conditions such as traumatic brain injury, cognitive impairment from schizophrenia and heart failure. The test is also used in hospitals to determine whether patients should be allowed to live alone or with a home aide. **(32).**

Previous studies demonstrated that people with less than12 years of education tended to have worse performance on the MoCA. To correct for education level effects, 1point was added for participants with education less than12 years on their total MoCA score. According to previous studies patients with total MoCA score lessthan26 were diagnosed as PSCI **(29).**

Management of cognitive impairment:

Interdisciplinary Collaboration

Collaboration among physicians, including neurologists, gerontologists, and primary care physicians, speech language pathologists, occupational therapists, neuropsychologists, nurses, and related health professionals is crucial throughout levels of poststroke care for the optimal identification and management of cognitive problems after stroke. A tailored neuropsychological evaluation is best suited to thoroughly characterize cognitive strengths and weaknesses, which is important for optimal management of PSCI. This also will aid in individualizing care tailored to the patient's needs, such that involvement of all disciplines is not needed for all patients for example, speech-language pathologists can identify and treat cognitive and communication deficits after stroke (and dysphagia). Occupational therapists can further evaluate and manage the functional impact of cognitive problems in patients' daily activity contexts. A streamlined, interdisciplinary model of care beyond the acute and subacute phases after stroke is needed for optimal monitoring and management of cognitive deficits. Telehealth services might be a useful tool to implement such a model, provided that barriers to these services are addressed **(33).**

Cognitive Rehabilitation

In general, cognitive rehabilitation (including restorative cognitive training and functional cognitive rehabilitation) after stroke results in small improvements in cognitive functioning compared with control conditions (treatment as usual or active sham intervention) **(34)** small gains, both immediate and sustained, occur in several cognitive areas (attention, memory, executive function) and visuospatial neglect. Specifically, memory gains occur with strategy training **(35)** but attention training does not produce consistent benefits **(36).** Benefits of computerized cognitive training (e g, engaging and gamified cognitive exercises accessed from the patients' own computers or mobile devices) over standard cognitive rehabilitation are inconsistent but tend to be better with clinician-directed programs **(37)** emerging evidence, albeit from small or lower-quality studies **(38).** suggests potential cognitive benefits of virtual reality tools **(39)** and training and education for family and patients **(40).**

Physical Activity

Physical activity may have a positive impact on cognitive function after stroke, with a possible advantage for aerobic compared with nonaerobic exercise **(41).** Small studies suggest cognitive benefits of specific forms of physical activity such as boxing **(42)** and resistance exercises **(43)** evidence for the added benefit of using virtual reality with physical activity is inconclusive **(44).**

Medical and Pharmacological Treatments

Because the risk of PSCI increases with stroke recurrence, secondary stroke prevention, including antihypertensive therapy, statins, diabetes control, and anticoagulation for atrial fibrillation, is an important approach to prevent the risk for or worsening of PSCI **(45).**

Treatments for hypertension and lifestyle programs to reach target blood pressure after stroke have to date failed to show positive impacts on cognitive function **(46).** Current evidence is insufficient to prove whether some antihypertensive drug classes are better than others at preserving cognition **(47).** Nonetheless, hypertension treatment reduces the risk of incident and recurrent strokes, which are risk factors for PSCI. In the general population, blood pressure lowering with antihypertensive agents compared with control is associated with a reduced risk of cognitive impairment and incident dementia **(48).**

There are knowledge gaps in the effect of interventions for smoking, obesity, diabetes, hyperlipidemia, and obstructive sleep apnea for reducing the risk of PSCI, although they are generally considered to be additional important modifiable risk factors for preventing cognitive decline **(49).**

Simultaneous treatment of multiple vascular risk factors compared with only one or few was associated with a slower cognitive decline in a cohort of patients with AD and could improve or maintain cognitive functioning in at risk elderly people from the general population Similar studies of multiple simultaneous interventions are needed in patients with PSCI **(50).**

Because cognitive outcome has traditionally not been considered an outcome measure in randomized trials investigating the benefit of acute stroke treatments, limited evidence exists with regard to their effect on cognition, although it is postulated that PSCI would be decreased because of reduction in acute lesion size and improved functional outcome. The few studies that evaluated cognitive outcomes after acute stroke treatments suggest that intravenous thrombolysis and mechanical thrombectomy improve cognitive outcomes (compared with no treatment) but that these benefits are strongly associated with functional outcome **(51).**

Systematic reviews of dopamine agonists **(52)** and selective serotonin reuptake inhibitors **(53)** show no consistent beneficial effects on cognition after stroke. Individual small clinical trials have reported various pharmaceutical agents that may have a potential benefit on global cognition: neurotrophics (Cortexin) **(54)** peptides such as Cerebrolysin **(55)** and relaxin **(56).** citicoline (cytidine-5′-diphosphocholine) **(57)** and nitrates (glyceryl trinitrate) **(58).** Specific pharmaceuticals may affect defined aspects of cognition, including the effects of dopamine agonists on hemi-inattention and selegiline on attention and executive function **(59).**

Acetylcholinesterase inhibitors, including donepezil, galantamine, and rivastigmine, are labeled for use in AD dementia and may also be effective for vascular dementia and DLB ***(60).*** Acetylcholinesterase inhibitors can worsen behaviors in FTD, and there is insufficient evidence of efficacy in MCI. The goal of treatment with acetylcholinesterase inhibitors is to improve or stabilize memory and attention by inhibiting the breakdown of acetylcholine, a neurotransmitter released by cholinergic neurons in the basal forebrain, an area known to be affected by AD ***(61)***.

Memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is thought to work by blocking the effects of excess glutamate and by upregulating NMDA receptor expression. Memantine is indicated for use in moderate to severe AD, and there is also evidence to support off-label use in mild to moderate vascular dementia. Memantine has been shown to confer modest improvements in thinking, everyday functioning, behavior and mood ***(62)*** are sometimes prescribed for patients with dementia after stroke, although more work is needed to define the safety and efficacy of these drugs in this population **(63).**

Randomized trials provide moderate-quality evidence for small improvements in cognition, of uncertain clinical relevance, with donepezil, rivastigmine, galantamine, or memantine; however, they are complicated by adverse events (including dizziness and diarrhea) and patient discontinuation **(62).**

Emerging, Complementary, and Integrative Treatments Small studies have shown the benefits of remote ischemic conditioning for visuospatial, attention, and executive functions **(64)** and long-term (>6 months) global cognition **(65).** Further confirmatory studies with larger samples are warranted **(66).**

Several studies suggest potential benefit from transcranial magnetic stimulation and transcranial direct current stimulation (t DCS). In a meta-analysis of 15 studies (N=820 participants) of t DCS, compared with sham t DCS or control, anodal t DCS was associated with a small improvement in the general cognitive and attention performance but not with memory. Most of these studies, however, were of lower methodological quality and lacked sham tDCS and safety data **(67).**

Well-designed studies are needed to determine the potential benefits of neuromodulation in the treatment of poststroke cognitive deficits and to establish the optimal treatment protocols **(67).**

Acupuncture treatments may also have a positive effect on global cognition. However, a meta-analysis suggests that the majority of these studies were of low quality **(68).** The combination of acupuncture with other therapies (e g, cognitive or physical rehabilitation) may enhance the benefits of either alone **(69).**

Preliminary and exploratory studies suggest potential cognitive benefits from various herbal treatments and vitamins, including huperzine A**.** depsides salts from Salvia miltiorrhiza, ginkgo biloba, pomegranate polyphenols and Cerebral care Granule but no benefits from mailuoning folic acid, and B vitamins**.** None of these are approved by the US Food and Drug Administration for use in PSCI. Last, there is a paucity of randomized studies on the potential effects of heart-healthy diets (e g, DASH [Dietary Approaches to Stop Hypertension] diet, Mediterranean diet, MIND [Mediterranean-DASH Intervention for Neurodegenerative Delay] diet) on cognition after stroke **(23)**

Sleep: Behavioral interventions for sleep disturbance include counseling about sleep hygiene, light therapy, and referral for cognitive behavioral therapy for insomnia ***(70).***

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