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POST-STROKE DEMENTIA: FEATURES OF CLINICA-NEUROLOGI, NEUROPHYSIOLOGII IMMUNOLOGI, IMPROVEMENT OF REHABILITATION MEASURES

Khayriyeva Muxsina Farxodovna

PhD, assistant, Bukhara State Medical Institute, Bukhara, 200100,

Uzbekistan e-mail: abumkur14@gmail.com

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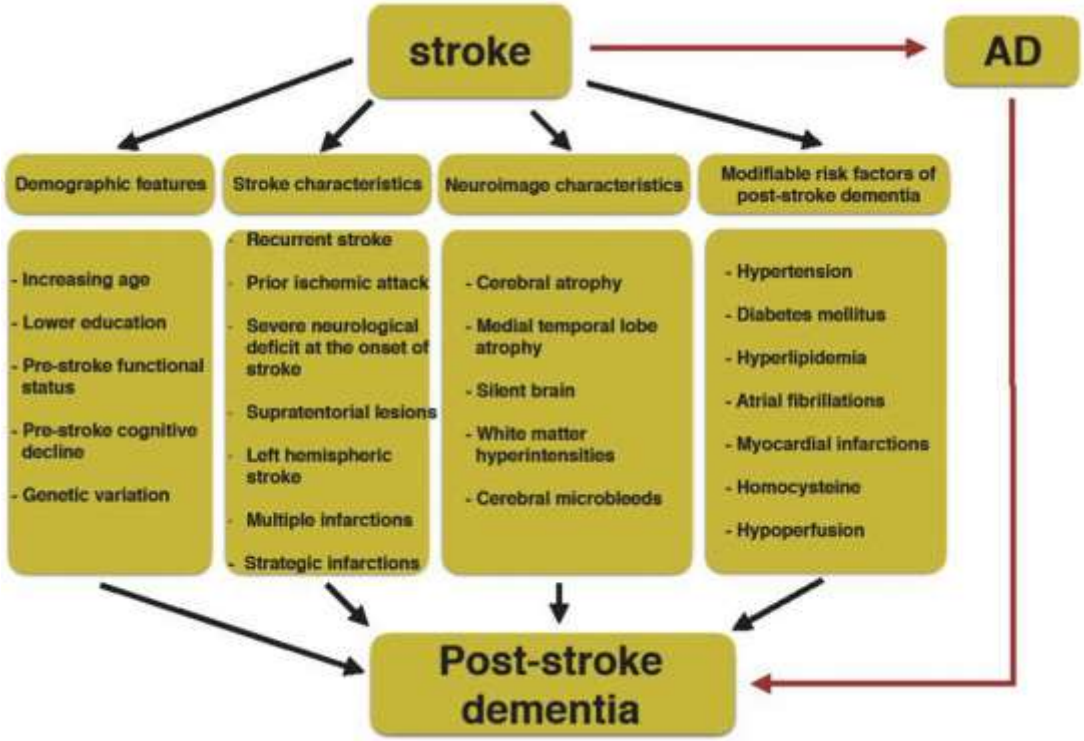
Annotation. Post-stroke dementia (PSD) is a clinical entity that encompasses all types of dementia following an index stroke, which may affect up to one third of stroke survivors. Unlike physical disability after stroke, cognitive function usually worsens over time and are often overlooked with detrimental impacts on the quality of life of survivors. The risk factors for post-stroke dementia are multifactorial and includes genetic predisposition, demographic factors (like older age and lower education status), pre-stroke cognitive and functional status, prior transient ischemic attack or stroke, vascular risk factors, characteristics and medical diseases associated with complications of stroke.

Key words: post-stroke, result, treatment, diagnosis, consequences

Neuroimaging determinants are global cerebral atrophy or regional atrophy like hippocampal atrophy or medial temporal lobe atrophy, white matter lesions and changes, silent infarcts, lacunar infarcts and microbleeds. The mechanism of post-stroke dementia remains unknown and its neuropathology is poorly defined. Post-stroke dementia patients may benefit from target treatment of dementia with anti-dementia drugs as well as prevention and treatment of strokes. This review focus on the epidemiology, presumed mechanisms, recent studies on biomarkers, diagnostic workup and promising management strategies with functional outcome for post-stroke dementia. Stroke is the leading cause of disability and the second leading cause for dementia worldwide. Out of approximately 15 million people suffering stroke every year; about 5 million, one third, are left with permanent disability.[1]A big increase in the prevalence of post-stroke dementia (PSD) has been

observed in recent years due to increase in stroke in aging population and to decline in mortality from stroke with modern treatments. Cognitive decline symptoms are often overlook in stroke survivors leading to increased rates of mortality and institutionalization. Because of their dependency and negative financial impact upon their families and healthcare providers, PSD is a major public health issue and its prevention playing the crucial role. This review article discusses the epidemiology, implications, risk factors, mechanism and current management strategies for PSD.



The dementia that occurs after a stroke, irrespective of the presumed cause, and the final diagnosis of PSD should be delayed to at least 6 months after stroke according to American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorder. PSD may impact all aspects of cognitive functions, but attention and executive function is the most affected domains. A study suggested that the presumed etiology of poststroke dementia was vascular dementia in two-thirds of patients and Alzheimer's disease in one-third. There are many studies about the incidence and prevalence of PSD but comparisons are difficult owing to variations in the criteria for the diagnosis of dementia, patient characteristics, stroke subtype, methodology, and duration of follow up. Various tools are available to screen and assess cognition, they are not PSD-specific. The most commonly used diagnostic criteria and tools are developed by National Institute of Neurological Disorder and Stroke-Vascular Cognitive Impairment (NINDS-VCI), Association Internationale pour la Recherché et l'Enseignement en Neurosciences for VaD and Diagnostic and Statistical Manual of Mental Disorders. The incidence of PSD over time course is non-linear, being higher in the first 6 months after stroke.[3]A study in Italy found that 21.5% patients developed dementia

after stroke during 4-year follow-up.[4]In the Rochester study, the relative risk of dementia after stroke was 8.8 after 1 year, then declined progressively to 4.2 after 3 years, 3·5 after 5 years, 2.5 after 10 years, and 2.0 after 25 years.5 In addition, many studies demonstrated that previous or recurrent strokes were correlated to a high risk of PSD.6, 7 A systematic and meta-analysis found that 10% of patients had dementia before the first stroke, 10% developed dementia soon after the first stroke and more than 30% had developed dementia after recurrent stroke.6 The prevalence of PSD ranges from 6 to 32% with the prevalence around 28% at 3 months point of time after stroke.[6, 7] Increasing age is commonly a recognized risk factor for PSD.8 There was no significant relationship between gender and the risk of PSD, although some found female sex to be higher risk. A lower education level was an independent predictor of PSD in most studies.[9] Pre-stroke functional and cognitive status prior to the stroke were also predictors for PSD.[10] Desmond et al. suggested that severe neurological deficit diagnosed at onset of stroke is associated with a high risk of PSD.[11] Other vascular risk factors such as hypertension, diabetes mellitus, atrial fibrillations, and myocardial infarctions are also independent risk factors of PSD.[12]Hypertension, the biggest risk factor for stroke, is also a leading risk factor for vascular dementia and Alzheimer's disease.[13] In the Framingham Heart Study, the chronicity of hypertension was inversely related to the cognitive functioning.[14] The Honolulu Asia Aging Study showed cognitive benefit from blood pressure lowering especially in the middle age Japanese–American men.[15] The Study also found that diabetes was associated with increased risk of total dementia (relative risk 1.5 [95% CI 1.01–2.2]), Alzheimer's disease (AD; 1.8 [1.1–2.9]) and vascular dementia (VaD; 2.3 [1.1–5.0]).16 The influence of hyperlipidemia, hyperhomocysteinemia, alcohol consumption, and cigarette smoking on PSD remains unproven. In addition, some studies have found that medical illnesses such as seizure, sepsis, arrhythmia, hypotension, and congestive heart failure might be associated with high risk of PSD.[17, 18]

Stroke pathogenesis and the neuroanatomical structures and locations determine the risk of PSD. In the Framingham study, large artery infarcts, lacunar infarcts, and infarcts of unknown origin were associated with high risk of PSD.[19] A systematic meta-analysis revealed hemorrhagic stroke also related to increased risk of PSD.6, [20] Chronic brain ischemia from hypoperfusion induced by a variety of cardiovascular deficits can cause nerve cells damage and protein synthesis abnormalities that might increase risk of further dementia.[11] Dementia can even be caused by non–focal neurological changes found in patients with transient ischemic attack (TIA).[2] In addition neuroimaging studies suggested that infarction in strategic locations in the brain plays an important role in the risk of PSD. These lesions include infarctions at dominant thalamus, angular gyrus, deep areas of frontal lobe, medial temporal lobe, hippocampus and left hemispheres to multiple infarctions in both brain hemispheres.

The neuroimaging abnormalities correlating with PSD are cerebral atrophy, silent and multiple infarctions, white matter lesions, and cerebral microbleeds commonly seen by computerized tomography (CT) and magnetic resonance imaging (MRI). Laakso et al. found medial temporal atrophy both in vascular dementia and Alzheimer's disease.[4]Silent brain infarction is the finding of cerebral infarction on brain images in the absence of stroke clinical symptoms. The Rotterdam Scan Study found silent brain infarcts as an independent predictor of PSD.[5] Severe white matter changes on neuroimages indicates increased risk of PSD.[6] These White matter hyperintensities may be caused by a variety of factors including ischemia, gliosis, micro-hemorrhages and damage to small blood vessel walls. Pantoli suggested that both white matter lesions and lacunar infarctions are predictors of cognitive decline after stroke.[17]In addition, two large studies also showed that multiple cerebral microbleeds are associated with cognitive impairment in stroke survivors.

Functional imaging by Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) evaluates the cerebral blood flow and glucose metabolism and is useful in the differentiation between vascular dementia and Alzheimer's disease. A large cohort study using positron emission tomography showed that increased Alzheimer's disease-like Pittsburg compound B retention and medial temporal atrophy were associated with dementia after stroke/TIA.[10] Liu et al. used Pittsburgh Compound B (PiB) positron emission tomography to investigate patients with stroke or TIA who had a more progressive cognitive decline. They found that concurrent amyloid pathology was found in about one fifth of the patients.

Functional magnetic resonance imaging (fMRI) can detect disruption of cholinergic pathways and major hubs of large-scale networks in patients with PSD.[12] Additionally, advanced multi diffusion tensor imaging (DTI) has been shown to better correlate with cognitive deficits (particularly executive functions) supporting the notion that cognitive dysfunction in the vascular cognitive impairment (VCI) spectrum is due to the disruption of subcortical white matter pathways. One longitudinal study demonstrated the predictive value of DTI for cognitive decline as well as atrophy of mesial temporal lobe.

Genetic factors might be independent risk factors of PSD. Most of them are related to lipid metabolism, angiotensin, and inflammation.[5] Genes such as a-1-antichymotrypsin polymorphism, angiotensin-converting enzyme gene and Apolipoprotein E (APOE) gene have been studied.[16, 17] There is evidence showing APOE e4 is associated with the risk of AD and vascular cognitive impairment.[18] Morris et al. found that NOS3 TT genotype increased the risk of incident dementia compared with the GG genotype.[19] The most common form of inherited vascular dementia is cerebral autosomal dominant (CADASIL) and cerebral autosomal recessive arteriopathy with

subcortical infarcts and leukoencephalopathy (CARASIL) which are linked to NOTCH3 and HTRA1 gene

The sensitive CSF biomarkers for Alzheimer's disease, such as Aβ-42 peptide and tau protein, show lowest specificity for vascular dementia. Recent studies showed significantly elevation of matrix degrading metalloproteinases (MMPs) such as gelatinase B (MMP-9) in vascular dementia. Other CSF markers associated with vascular dementia and indirectly PSD are α-1 antitrypsin, plasminogen activator inhibitor-1, and apolipoprotein H.40 Serum biomarkers such as advanced glycation end products (sRAGE), b-secretase enzyme (BACE1) and APOE genotypes have been suggested to correlate with poststroke cognitive impairment.41 A common variant (29.5%) (polymorphism) of alpha-2-macroglobulin leads to increased risk of Alzheimer's disease. Currently, no specific biomarkers have been proven to discriminate Alzheimer's disease from PSD.

The mechanism of PSD remains unclear. The pathological substrates associated with post-stroke or vascular dementia are poorly understood and remain controversial for several reasons. There is considerable overlap between the neuropathological data of cerebrovascular disease and Alzheimer's disease.[14] The heterogeneous nature of cerebrovascular lesions may have an effect on cognition through various mechanisms including altered blood flow and oxygen supply, chronic inflammation, disruption of axonal tracts, or altered cortical connectivity. Some studies provide the pathological evidence of a substrate (clasmatodendrosis), which contributes to the development of dementia in stroke survivors, mostly of vascular origin. The clasmatodendrosis (morphological attribute of irreversibly injured astrocytes) was reported to link to white matter hyperintensities and frontal white matter changes. These clinicopathological findings provide a novel association between irreversible astrocyte injury and disruption of gliovascular interactions at the blood–brain barrier in the frontal white matter and cognitive impairment in elderly post-stroke survivors. The neuritic plaque which is one of the main pathologic manifestations of Alzheimer's disease increased as the aggravation of atherosclerosis suggesting the correlation between stroke and Alzheimer's disease.

Medical comorbidities can cause cerebral hypoxia or ischemia leading to cerebral hypoperfusion, which serves as a basis for some cases of PSD.[18] Gasecki et al. suggested that decline in cerebrovascular reserve capacity and increased vascular degenerative changes in hypertensive patients may lead to the development of micro-hemorrhages, micro-infarcts, and hyper-dense white matter lesions. It can also affect the cerebral vaso-reactivity and auto-regulatory capacity. Zhang and colleagues found that diabetes-exacerbated PSD might be associated with abnormal phosphorylation of tau and generation of amyloid beta in the brains of animal models

Inflammatory and immune processes are directly involved in the pathogenesis of PSD. A study demonstrated that decreased cytokines such as interleukin-6 and interleukin-8 are associated

with changes in both gray and white matters, suggesting inflammatory and immune factors contributing to the pathogenesis of dementia per se. The possible biomarkers reported having an association with dementia were tumor necrosis factor-α, interleukin-1, interleukin-10, sE-Selectin, vascular endothelial cell adhesion-1, nerve microfilament proteins, α-Synuclein, and γ-Synuclein.46 In a recent study, patients with vascular dementia were found to have increased serum somatostatin and decreased neuron-specific enolase with the lower content than that in control group up to 6 months after stroke.

Prevention of primary and secondary stroke is of utmost importance in PSD management strategies. Aggressive management of pre-stroke risk factors by medications and lifestyle changes plays important role in the prevention for PSD. Antiplatelet or anticoagulant, antihypertensive and lipid-lowering agents are commonly used to treat risk factors. Early and optimal treatments for strokes when they occur and early rehabilitation are the next crucial intervention. In addition, cognitive impairment can benefit from treatment of neuropsychiatric symptoms as well as cognitive training.

Several controlled trials have showed that antihypertensive medication could decrease the risk both vascular dementia and Alzheimer's disease. The exact mechanism is unclear but could be either due to a neuroprotective effect or result of pressure lowering by antihypertensive medication. Most studies suggested angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and calcium channel blockers prevent cognitive decline in patient with hypertension. Blockade of the renin–angiotensin system by angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors can prevent onset of dementia. Inhibiting of neuronal calcium influx by calcium channel blockers can have a protective effect on cognitive decline as the disturbance of the intracellular calcium homeostasis is central to the pathophysiology of neurodegeneration. A systematic review showed four randomized controlled trials had benefit of antihypertensive drugs on cognitive decline: SYST-EUR (Systolic Hypertension in Europe Study) I and II, with a 55% reduction in dementia risk; HOPE (Heart Outcomes Prevention Evaluation), with a 41% reduction in cognitive decline associated with stroke; and PROGRESS (Perindopril Protection against Recurrent Stroke Study), with a 19% reduction in cognitive decline.

In conclusion, chronic brain changes related with advancing age compromise the cognitive reserve and increase the risk of post-stroke dementia (PSD) when vascular attacks occur or recur. After intervention for acute stroke, early and optimal intervention should be directed to post-stroke dementia (PSD) in the window before dementia sets in. Detailed clinical and neuropsychological assessment after stroke is the crucial in order to estimate the prognosis and program for secondary prevention. The current barriers for earlier identification of PSD is lack of uniform diagnostic criteria, PSD-specific assessment tools and precise biochemical marker. Lastly, future researches

might shed light on the pathophysiology and might come up with new diagnostic neuroimaging techniques and bio-markers in addition to cognitive assessment tool for early recognition of PSD.

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