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Stroke and cognitive impairment

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Post-stroke cognitive impairment (PSCI) is known to be accompanied in about 10% first-ever stroke, and 30% in recurrent stroke.[1] In patients with intracerebral hemorrhage, the incidence of new-onset dementia was observed in 14.2% in 1 year, 28.3% at 4 years after hemorrhage.[2] However, the prevalence and incidence might vary according to time intervals between index-stroke and cognitive evaluations and research setting such as community- or hospital-based study.[1] Risk factors for PSCI are almost non-modifiable factors; age, education, lesion extent, lesion location, index-stroke severity, and amyloid imaging positivity. Modifiable risk factors during both acute stroke and chronic stage remained to be investigated.

1. Clinical characteristics of post-stroke cognitive impairment

PSCI could develop early (3 months) or delayed (several years) after index stroke. Their pathophysiology is known to be different according to temporal profile; early PSCI was associated with index-stroke related factors, and delayed PSCI was with superimposed amyloid pathology.[3] Stroke survivors with positive amyloid imaging showed poor cognitive trajectories compared to those without amyloid positivity. These interactions shed light on the pathophysiology of delayed cognitive decline after index-stroke. These findings might give perspective to future therapeutic trials, and new classification systems might incorporate these interactions between vascular insult and amyloid process within the scheme. However, it was not thoroughly investigated yet that stroke might accelerate neurodegenerative process yet.

PSCI is often classified as multi-infarct dementia and strategic-infarct dementia.[4] Multi-infarct dementia is dementia syndrome caused by recurrent and multiple infarctions, and stroke lesion extent and severity determined the neuropsychological construct. In contrast, strategic-infarct dementia is caused by relatively small lesion, which is strategically located in functionally-important location such as anterior limb or genu of internal capsule, caudate nucleus, thalamus, medial frontal lobe, inferomedial temporal lobe, and angular gyrus.

2. Clinical evaluation in patients with PSCI

For proper evaluations of PSCI, somewhat different approach is needed compared to those in patients with

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AD dementia. Most stroke survivors have stroke sequelae such as hemiparesis and dysarthria, these neurologic deficits might affect the proper neuropsychological evaluations. For the diagnosis of dementia, determination of activities of daily living impairment is important. However, due to above-mentioned stroke-sequelae, impairment of activities of daily living should be based on solely cognitive deficit, not based on physical barriers. Furthermore, most diagnostic criteria did not give any specific cutoff values for 'cognitive impairment', thus various cutoffs such as below -1.5SD or 10%ile from age-, education-adjusted mean, has been adopted in previous studies. Recently, VasCog statement and DSM-5 has suggested below -2 SD as proper criteria for 'cognitive impairment'.

There are various tools to evaluate cognitive function in patients with stroke. Montreal cognitive assessment (MoCA) is a brief screening tool, and it could be conducted in around 15 minutes. It had alternating trail making, cube, and clock tasks, which improve sensitivity to detect frontal dysfunction. However, MoCA require intact motor and visual function, patients with hemiparesis or visual field defect could not complete the test properly. Several tests, which are 5-minute National Institute of Neurological Disorders and Stroke-Canadian Stroke Network protocol and Six-Items Screener, are consisted of only verbally conducted tasks, and are capable to be conducted in those with dominant hand weakness and visual field defect.

In cases of below age-, educated-adjusted norm in brief screening test, detailed neuropsychological tests are required to identify domain-specific cognitive impairment and magnitude of deficits. For those with PSCI, National Institute of Neurological Disorders and Stroke-Canadian Stroke Network has proposed the Vascular Cognitive Impairment Harmonization Standard - Neuropsychological Protocol (VCIHS-NP) as standard tests to evaluate cognitive function.[5] It is consisted of 5-, 30-, and 60-minute protocol, and 5-minute protocol is a constellation of subtests of MoCA.

3. Diagnostic criteria of PSCI

There were various proposals for definition, classification, and diagnostic criteria for vascular cognitive impairment (VCI). Until now, the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche ′et l'Enseignement en Neurosciences (NINDS-AIREN) criteria has been the most commonly used criteria in practice and researches.[6] According to the criteria, impairment of memory and of two or more cognitive domains are required for the diagnosis of vascular dementia. Cerebrovascular disease should be accompanied, which is defined by the presence of focal signs on neurologic examination consistent with stroke, and evidence of relevant cerebrovascular disease by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct as well as multiple basal ganglia and white matter lacunes or extensive periventricular white matter lesions, or combinations thereof. In addition, a relationship between the above two disorders should be manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

Like these criteria, classical diagnostic criteria should be accompanied by memory deficit. Due to accumulating evidences about clinical characteristics of VCI, the preferential decline in attention/frontal executive function was emphasized in early diagnosis of VCI. These findings incorporated in the recently proposed diagnostic criteria such as American Heart Association-American Stroke Association statement, VasCog statement, and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.[7] According to AHA-ASA criteria, vascular dementia is defined as cognitive impairment at least two cognitive domain regardless of memory deficit along with imaging evidence of cerebrovascular disease and a clear temporal relationship between a vascular events and onset of cognitive deficit or clear relationship in the severity and pattern of cogni-

tive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology.[7] Cognitive tests should include a minimum of 4 cognitive domains: executive/attention, memory, language, and visuospatial functions.

In addition to AHA-ASA criteria, recently proposed the DSM-5 also removed the prerequisites of memory impairment for diagnosis of VCI in contrast with former DSM-4 criteria. Looking further ahead, VasCog statement extended the concept of vascular dementia defining it as cognitive deficits in only one cognitive domain if activities of daily living are impaired.[8] Besides that, VasCog statement further specified the criteria for cognitive impairment as below -2 standard deviation from age-, education-adjusted norm. Until now, other diagnostic criteria did not specify the threshold of cognitive impairment, thus several criteria of -1.5SD, -2SD, and 10%ile have been used by clinicians and researchers.

4. Neuroimaging biomarkers and pathophysiological perspectives

Recent advances in neuroimaging technique shed light on the pathophysiology of PSCI. In addition to traditional neuroimaging biomarkers such as lacunar infarction, leukoaraiosis, microbleeds, and medial temporal lobe atrophy, the multimodal imaging including diffusion tensor imaging and resting-state functional MRI gave an insightful data. Dysfunctions in neurovascular unit dysfunction and blood-brain barriers, cortical microinfarction, and cerebral amyloid angiopathy is also intriguing topics in recent neuroimaging research fields.

Acute stroke in specific region might cause system-wide consequences. In previous study using resting-state functional MRI, the resting activity of default-mode network was altered in patients with acute stroke compared to control group, and this alteration was correlated with cognitive test score, line cancellation test score.[9] Lesion-mapping study also showed that strategically-located lesions which located at the major hubs of default mode network might increase the risk of post-stroke dementia.[10] These studies suggest the importance of large-scale functional neural network for the pathophysiology and as a biomarker of PSCI.

Small vessel disease is also thoroughly investigated for its pathophysiological role for VCI. Recently, intriguing studies of SVD broaden our understanding of complex interactions among chronic ischemic pathology, neurodegenerative process, and human cognitive function. Quantification of cholinergic pathway disruption by strategically-located white matter hyperintensities was proposed by Bocti et al. [11] In another study, subcortical cholinergic pathway disruption was associated with the development of post-stroke dementia, and impair the frontal cognitive function.[10,11]

Furthermore, several studies investigating the multimodal imaging in patients with crebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), one could get an insight for the longitudinal associations between white matter hyperintensities and lacunar infarction. Circulatory insufficiency in the periphery of deep medullary artery in brain parenchyma may aggravate the white matter hyperintensities, and newly-developed lacunar infarctions were frequently observed in the distal part of these arteries.[12] In addition, lacunar infarction located in the anterior thalamic radiation, forceps minor caused the regional atrophy of corresponding cortical regions, and finally frontal executive dysfunction.[13]

These sequential processes might give us a glimpse of how subcortical vascular dementia and strategic infarct dementia could be developed by incident ischemic lesions.

Superimposed amyloid pathology also showed complex interactions with vascular lesions. Patients with mixed PSCI, who had positive amyloid imaging by amyloid PET at index-stroke, had followed up for 3 years after stroke. They showed poor cognitive outcome assess by MMSE or MoCA compared to patients with pure PSCI who did not have amyloid pathology by imaging.[3]

5. Prognosis and natural course

Longitudinal studies showed various trajectories in PSCI. One study showed that 78% patients were stable, 14%

were aggravated, and 8% were improved.[14] However, another study showed longitudinal trajectories were different according to cognitive domains; aggravation mainly in memory and executive function, and relatively preservation in visuospatial function and language.[15] Likewise, prognosis of PSCI might show various characteristics according to evaluation time and tools.

Effect of stroke occurrence for longitudinal cognitive trajectories was identified in recent research published in JAMA in 2016. It has followed up 23,572 subjects who were aged over 45 years during 6.1 years.[16] In this study, stroke has caused abrupt decline in global cognition, new learning, and verbal memory at stroke onset, and cognitive decline has been accelerated in global cognition and frontal executive function compared with pre-stroke slopes.

Based on current evidences of longitudinal researches, stroke might cause abrupt decline of cognitive function and thereafter showed relatively stable course. However, there are some patients who showed continuous cognitive decline after stroke, and it might be caused by superimposed amyloid pathology or other premorbid neurodegenerative process. Recent study showed that age, diabetes mellitus, and severity of white matter hyperintensities and medial temporal lobe atrophy is associated with delayed cognitive decline after stroke during 4-year follow-up.[17]

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