

Post-stroke cognitive impairment: epidemiology, mechanisms and management

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Abstract: Post-stroke cognitive impairment occurs frequently in the patients with stroke. The prevalence of post-stroke cognitive impairment ranges from 20% to 80%, which varies for the difference between the countries, the races, and the diagnostic criteria. The risk of post-stroke cognitive impairment is related to both the demographic factors like age, education and occupation and vascular factors. The underlying mechanisms of post-stroke cognitive impairment are not known in detail. However, the neuroanatomical lesions caused by the stroke on strategic areas such as the hippocampus and the white matter lesions (WMLs), the cerebral microbleeds (CMBs) due to the small cerebrovascular diseases and the mixed AD with stroke, alone or in combination, contribute to the pathogenesis of post-stroke cognitive impairment. The treatment of post-stroke cognitive impairment may benefit not only from the anti-dementia drugs, but also the manage measures on cerebrovascular diseases. In this review, we will describe the epidemiological features and the mechanisms of post-stroke cognitive impairment, and discuss the promising management strategies for these patients.

Keywords: Post-stroke cognitive impairment; prevalence; risk factor; mechanism; treatment

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Introduction

Stroke, or cerebrovascular accident (CVA), which is also defined as the dysfunction of brain due to a disturbance of the cerebral blood flow, is the second most common cause of death and adult disability around the world (1). Because of the achievement of the public health and the medicine, the stroke mortality is falling down continuously. In 2008, the stroke death rate of America is 40.6 per 100,000 population, which is three fourths less than its historic 1931 to 1960 norm (2). Following by the decreased stroke death rate, more and more researchers pay attention to the disabilities that stroke survivors suffer from. There are 15 million people worldwide suffering from stroke every year, about 30% of which experience residual disabilities (3). It has been confirmed that stroke could result in the cognitive impairment. However, covered by the severe physical disability,

the post-stroke cognitive impairment is likely to be ignored.

In the past, the researchers identified the dementia after stroke as the vascular dementia (4). But not all stroke survivors who suffer from the cognitive decline meet the criteria of the dementia. As a result, the vascular cognitive impairment (VCI) took over the past “vascular dementia”. However, there’s evidence suggesting that the cognitive impairment after stroke is involved in not only the VCI, but also the pathogenesis of Alzheimer’s disease (AD). The clinical study suggested that the pathogenesis of AD make contributions to the 1/3 demented cases after stroke (5). Thus there’s an overlap between VCI and AD. According to the autopsy study, approximately 50% of dementias are attributed to both VCI and AD (6).

According to Nys *et al.*, a high proportion of stroke survivors had met the cognitive impairment within 3 months

after stroke (7). Although the prevalence of post stroke cognitive impairment is very high according to the present data, there's still evidence showing that the present criteria may underestimate the frequency of the dementia and the cognitive decline in stroke survivors (8,9). These patients with the cognitive impairment could be divided according to the degree of the cognitive decline into the mild cognitive impairment and dementia. Interestingly, in different studies, the dementia ratio within 3 months after stroke varies from 6% to 27% (10,11). The variety of the conclusion may be due to the different application of the criteria of the dementia or the cognitive impairment. The present standard criteria of the dementia include the diagnostic and statistical manual of mental disorders IV (DSM IV), international classification of disease-10 (ICD-10) and national institute of neurological and communicative disorders and stroke and the AD and related disorders association (NINCDS-ADRDA) criteria. Besides the demented patients, the degree of the cognitive decline of other cognition-impaired patients who fail to meet the above criteria could be measured by the yardsticks such as the mini-mental state examination (MMSE) score, Montreal cognitive assessment scale (MoCA) score, the abbreviated mental test, AD assessment scale-cognitive (ADAS-Cog) and so on. Of course, there are some other measures which are mainly originated from the above yardsticks. For example, the six-item screener (SIS) is a brief cognitive function test which is derived from the MMSE and designed for either in-person or telephone administration. What's more, multiple neuropsychological test batteries are used to examine not only the total cognitive function but also the level of impairment on every single cognitive domain like memory, language, visuoconstruction, executive function, calculation, comprehension and judgment.

In this review, we include the new evidence regarding the epidemiology of post-stroke cognitive impairment and discuss its potential risk factors. The mechanisms that could underlie the cognitive impairment after stroke are discussed, including the impaired neuroanatomical structures and the cerebral microbleeds (CMBs) which may result in VCI, and the contribution of stroke to AD. Finally, we critically review the present promising treatment to post-stroke cognitive impairment.

Epidemiology

Prevalence of post-stroke cognitive impairment

The prevalence studies focus on the whole population

who show the cognitive impairment after stroke. Although these studies in community or hospital settings always fail to exclude the patients who have suffered the cognitive decline before the stroke, they have shown the seriousness of the problem. The cross-sectional study widely proceeded in ten countries suggests that about 30% ischemic stroke survivors show a cognitive impairment which is determined by the MMSE score is lower than 27 (12). But the results of the studies vary for the difference between the countries, the races, and the diagnostic criteria. In Europe, such as Britain and Sweden, the prevalence of the cognitive impairment 3 months after stroke ranges from 24% to 39% according to the MMSE, while the prevalence in the same population is up to 96% according to the comprehensive neuropsychological test batteries (13,14). And In Netherland, the Maastricht CODAS which examined the cognitive function of 176 subjects with the first-ever stroke after 6 months by MMSE has suggested that the prevalence of cognitive impairment is up to 70% (15). One study on patients with a first-ever stroke and TIA admitted to the hospital in Norway suggested that 57% stroke patients suffered from the cognitive impairment during the first year after stroke (16). Recently, a study based on the cohort of first-ever stroke patients without pre-stroke dementia in France suggested that the frequency of the cognitive impairment 3-month after stroke was 47.3% (17). In Australia, the studies have shown that cognitive impairment prevalence 3 months after stroke is 50% to 58% according to a series of neuropsychological tests (18,19). What's more, the study also suggests that the cognitive impairment on the stroke survivor exist on any single domain such as attention, spatial ability, language and executive ability more frequently than the multiple domains (20). In America, the study on 212 subjects from the Framingham Study suggested that 19.3% of cases developed into the dementia in 10 years after stroke (21). One study suggested the prevalence of post stroke cognitive impairment in Mexican Americans was higher than in non-Hispanic whites and about 31% stroke patients of Mexican American would suffer from the post stroke dementia (22), showed that there was a difference between the regions and the races. What's more, in Caribbean, Chausson *et al.* examined the cognitive function of 293 stroke patients 5 years after the first-ever stroke from the cohort of ERMANCIA study in Martinique and suggested that 58.9% patients suffered from the cognitive impairment (23). In Asia, the study conducted by Yu *et al.* in South Korea suggested the highest result of all. Proceeding in 12 hospitals in South Korea which

enrolled 620 patients with ischemic stroke, it proposed that the prevalence reached up to 69.8% 3 months after stroke as measured by Korea MMSE (24). The study on 252 Singaporean patients within 6 months post-stroke showed that 44% patients suffered from the cognitive decline, while the prevalence declined to 34% in 1-year follow-up (25). The later prospective study in India showed that the prevalence of cognitive impairment was about 20% in total stroke survivors (26). In China, the study on 179 cases with 3 months after stroke in Hong Kong suggested that the prevalence of cognitive impairment after stroke was 21.8% as measured by MMSE, which would decline to 18% after the removal of previous stroke cases from the sample (27). Zhou *et al.* examined the cognitive function of 434 patients with stroke by 1-year follow-up in Chongqing. The study suggested a 37.1% of cognitive impairment prevalence 3 months after stroke (28). What's more, one recent study proceeding in Changsha which included 689 ischemic stroke patients detected that the prevalence of post stroke cognitive impairment was 41.8% (29) (Table 1 and Figure 1).

Risk factors of post-stroke cognitive impairment

The risk of the cognitive impairment after stroke is associated with the overlap of the frequent cerebrovascular disease and the dementia. According to the demography, the age and the education level are related to the post-stroke cognitive impairment risk. The age is the risk factor of not only the stroke but also the cognitive decline. There's evidence suggesting that the prevalence of the cognitive decline after stroke would increase exponentially as age increases after 65 years old (30). The education level is a conflictive risk factor. It could influence the expression of the cognitive impairment in patients. The cohort study conducted by Elbaz *et al.* on 4,010 participants suggested the higher education was associated with the better cognitive performances (31). Furthermore, Wu *et al.* divided 206 patients who suffered from the ischemic stroke into the VCI group and the no-VCI group and examined MoCA score. The result suggested that the sensitivity of MoCA and the number of impaired MoCA factors decreased as the increase of the education level. The score of orientation factor in highest education level patients both with and without VCI is a full score. It seems that the higher education level could increase the tolerance of the cognitive decline (32). However, the education level has no effect on the rate of the aggravation of the cognitive impairment. Singh-Manoux *et al.* and Zahodne *et al.* each researched

the influence of education on the cognitive impairment with the two samples of 7,454 individuals from the Whitehall II cohort study and 1,023 participants in the Victoria Longitudinal Study. Both studies suggested that there was no significant difference of the rate of decline in cognitive function between each groups of the education level (33,34). Moreover, there's evidence suggesting that the occupation have effects on the prevalence of the cognitive impairment. Singh-Manoux *et al.* also suggested that the individuals with high occupations which were defined as the administrative positions had a more obvious cognitive decline than other occupations (33). Another study conducted by Douiri *et al.* proposed a higher prevalence of cognitive impairment after ischemic stroke in the manual workers (14).

Vascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation, and smoking increase the risk of both the cognitive impairment due to VCI or AD and the stroke (35). In addition, one recent study suggested that the recurrent stroke or the existing cerebral lesions would increase the prevalence of the cognitive impairment (36). The prevalence of the new-onset dementia in first stroke is about 10%, which in the recurrent stroke is 30%. The study conducted by Sibolt *et al.* included 486 patients with ischemic stroke, 115 of which met the dementia criteria of the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition criteria. The study showed that patients who had been diagnosed as dementia after stroke would suffer from recurrent stroke earlier than those without dementia, suggesting that the dementia after stroke was associated with increased risk for recurrent stroke (37). It seems that the post-stroke cognitive impairment and the recurrence of stroke could cross as a basis for the aggravation. These evidences support that the vascular therapy would benefit the recovery of the post-stroke impairment.

Mechanisms

The mechanism of post-stroke cognitive impairment remains uncertain. Either VCI or AD promoted by stroke may be the reason of post-stroke cognitive impairment, and evidence suggesting that sometimes they work on the post-stroke cognitive impairment together (Figure 2).

Vascular cognitive impairment (VCI)

Lesions on neuroanatomical structure

Since the past studies, the dementia after stroke has been

Table 1 The studies on post-stroke cognitive impairment

Location and year	Population	Measured duration after stroke	Sample size	Outcome measure	Results	Reference
Sweden, 2011	Patients admitted to a geriatric stroke unit at Sahlgrenska University Hospital in Sweden after a stroke	38 days	Stroke: 74, control: 49	MMSE; neuropsychological test battery	39% with cognitive impairment as measured by MMSE; 96% with cognitive impairment as measured by neuropsychological test battery	Gutierrez Perez et al. (13)
Britain, 2013	Patients from South London Stroke Register	3 months; annual follow-up	271, 817 individuals with 63% white, 28% black	MMSE; abbreviated mental test	24% with cognitive impairment 3 months after stroke; 22% with cognitive impairment relatively unchanged and at annual follow-up	Douiri et al. (14)
Netherlands, 2004	Patients with a first-ever brain infarct from cognitive disorders after stroke	1 month; 6 months; 12 months	176	MMSE; neuropsychological test battery	10.8% with dementia and 71.1% with MCI at 1 month; 7.7% with dementia and 61.3% with MCI at 6 months; 7.7% with dementia and 51.5% with MCI at 12 months	Rasquin et al. (15)
Norway, 2011	Patients with a first-ever stroke or TIA, transient ischemic attack admitted to the stroke unit of Asker and Bærum Hospital	12 months	206	MMSE; the clock drawing test, TMT A and B, 10-word test, ADAS-Cog	19.6% with dementia and 37.5% with MCI	Ihle-Hansen et al. (16)
France, 2014	Patients with the first-ever stroke and no pre-stroke dementia from Neurology Department of Dijon, University Hospital	3 months	220	MMSE; MoCA	47.3% with the post-stroke cognitive impairment, including 7.7% with dementia	Jacquin et al. (17)
Australia, 2004	Patients with and without mild-to-moderate first-ever stroke from North East Melbourne Stroke Incidence Study	1 year	Stroke: 99, control: 99	S-MMSE; IQCODE; IDA; DSM-IV	12.5% with dementia and 37.5% with cognitive impairment no dementia at 12 months	Srikanth et al. (19)
Australia, 2006	Patients from Sydney Stroke Study	3-6 months	Stroke: 169, control: 103	MMSE; NART-IQ; ADL; IADL; IQCODE; SOFAS	21.3% with dementia and 36.7% with MCI	Sachdev et al. (18)

Table 1 (continued)

Table 1 (continued)						
Location and year	Population	Measured duration after stroke	Sample size	Outcome measure	Results	Reference
United States, 2004	Subjects with stroke and non-dementia from the Framingham Study	10 years	212	DSM-IV	19.3% with dementia at 10 years follow-up	Ivan <i>et al.</i> (21)
United States, 2014	Subjects with stroke of Mexican American from Brain Attack Surveillance in Corpus Christi Project	90 days	513 for neurological outcome; 510 functional outcome; 415 for cognitive outcome	3MSE; IQCODE; ADL and IADL	31% with dementia	Lisabeth <i>et al.</i> (22)
Martinique, 2010	Patients with the first-ever stroke from the cohort of ERMANCIA study	5 years	293	MMSE	58.9% with cognitive impairment	Chausson <i>et al.</i> (23)
South Korea, 2012	Patients with the ischemic stroke from 12 hospitals	3 months	620	MMSE; IQCODE	69.8% with cognitive impairment	Yu <i>et al.</i> (24)
Singapore, 2002	Survived patients with TIA or stroke	Baseline: 6 months; follow-up: 1 year	Baseline: 252; follow-up: 155	MMSE; vascular dementia battery	Baseline: 40% with cognitive impairment without dementia; 4% with dementia; follow-up: 29% with cognitive impairment without dementia; 4% with dementia	Tham <i>et al.</i> (25)
India, 2013	Stroke survivors from the Kolkata	Annual follow-up	Baseline: 281; 1st year: 219; 2nd year: 180; 3rd year: 158	BMSE; ADL	Baseline: 13.88% with dementia; 6.05% with MCI; 1st year: 10.05% with dementia; 5.48% with MCI; 2nd year: 13.89% with dementia; 4.44% with MCI; 3rd year: 17.72% with dementia; 3.16% with MCI	Das <i>et al.</i> (26)
Hong Kong, 2006	Stroke patients admitted to Acute Stroke Unit of Prince of Wales Hospital	3 months	Total stroke cases: 179, first-ever	IQCODE; MMSE; DSM-IV	21.8% with cognitive impairment in total stroke cases; 18% with cognitive impairment in first-ever stroke cases	Tang <i>et al.</i> (27)

Table 1 (continued)

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Location and year	Population	Measured duration after stroke	Sample size	Outcome measure	Results	Reference
Chongqing, 2005	Patients with ischemic stroke admitted to Daping Hospital of Chongqing city	3 months	434	MMSE; IQCODE	37.1% with the post-stroke cognitive impairment; 32.2% with the stroke-related cognitive impairment; 29.6% with the cognitive impairment after first-ever stroke	Zhou et al. (28)
Changsha, 2014	Patients with ischemic stroke from the communities	3 months	706	MMSE; MoCA; FAB; WMS; CDR; FAQ; ADL; CES-D; SSRS; NINDS; AIREN	41.8% with cognitive impairment after ischemic stroke	Tu et al. (29)

Abbreviation: MCI, mild cognitive impairment; MMSE, mini-mental state examination; 3MSE, modified mini-mental state examination; S-MMSE, standardized Mini-Mental state examination; IQCODE, informant questionnaire for cognitive decline in elderly; ADAS-Cog, Alzheimer's disease assessment scale-cognitive; IDA, irritability, depression and anxiety scale; DSM-IV, diagnostic and statistical manual of mental disorders criteria, 4th edition; NART-IQ, national adult reading test-intelligence quotient; ADL, activities of daily living; IADL, instrumental activities of daily living; SOFAS, social and occupational functioning assessment scale; BMSE, Bengali version of Hindi mental state examination; MoCA, Montreal cognitive assessment; fab, frontal assessment battery; WMS, Wechsler memory scale; CDR, clinical dementia rating; FAQ, functional activities questionnaire; CES-D, center for epidemiological survey-depression scale; SSRS, social support rating scale; NINDS, national institute of neurological disorders and stroke; AIREN, association internationale pour la Recherche et l'Enseignement en Neurosciences.

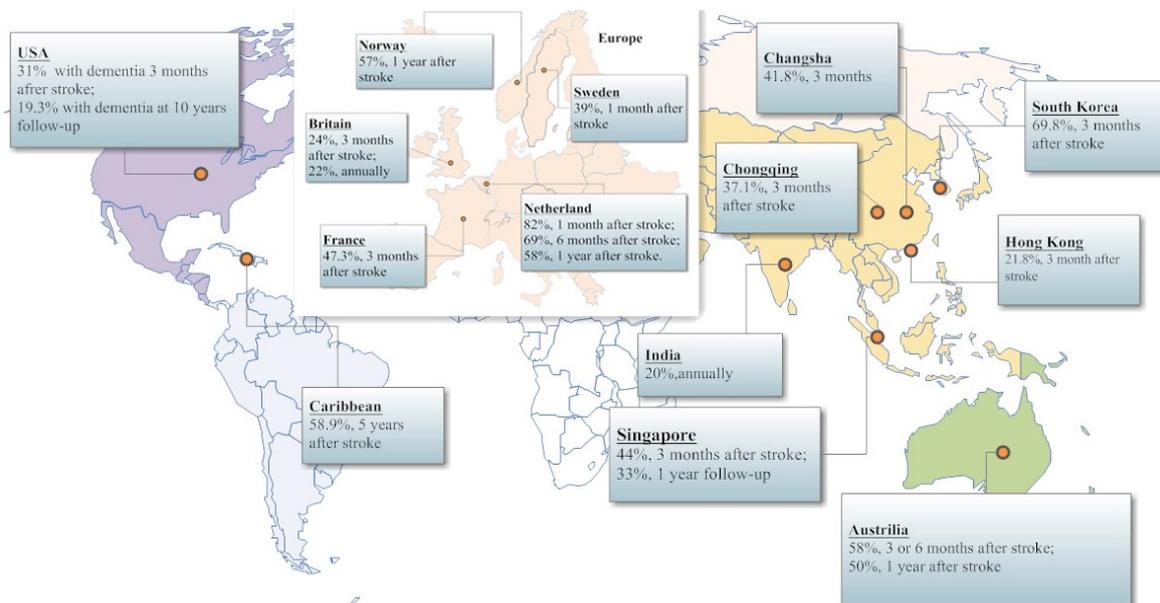


Figure 1 The distribution of the post-stroke cognitive impairment.

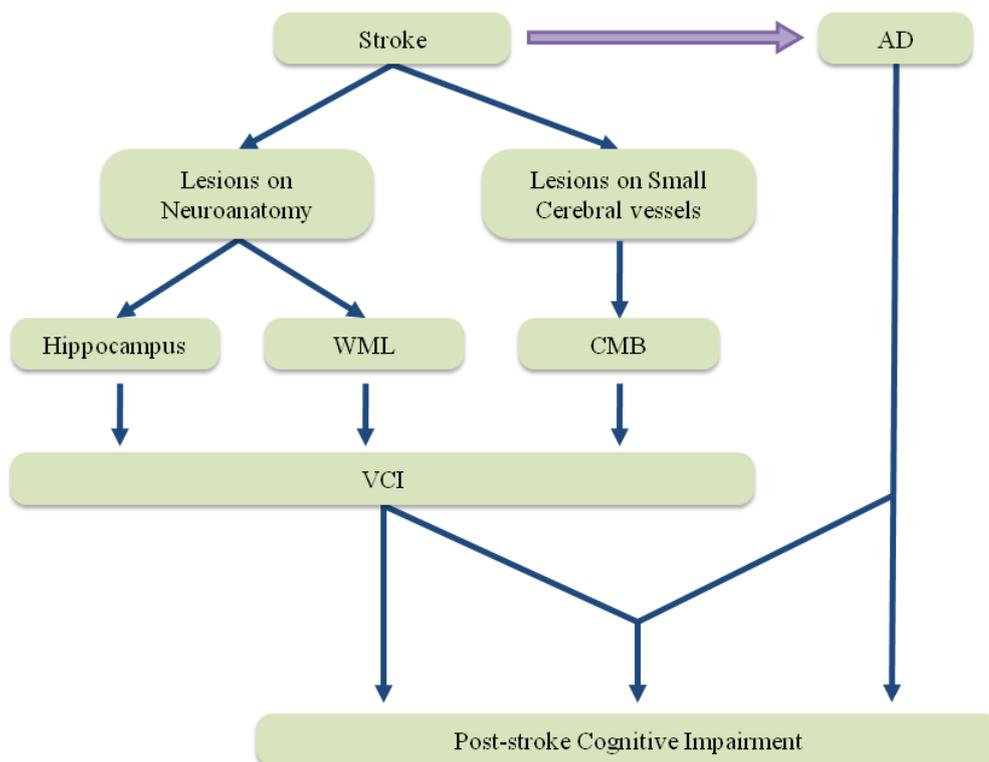


Figure 2 The main mechanisms on post-stroke cognitive impairment. AD, Alzheimer’s disease; WML, white matter lesion; CMB, cerebral microbleed; VCI, vascular cognitive impairment.

considered to be based on the neuroanatomical lesions caused by stroke. The study conducted by Tomlinson *et al.* in 1970 suggested the volume of infarcts was correlated the occurrence and development of cognitive impairment, which would cause the vascular dementia when being higher than 100 mL (38). But the recent study suggested that the total volume of infarcts explained only a small proportion of the variability of cognition in the stroke patients, and supported that infarcts in strategic areas played an important role in the mechanism of cognitive impairment after stroke and were associated with the severity of the dementia (39). It also suggested not the total infarcted volume but the infarcted volume in the strategic areas, such as cortical limbic areas, heteromodal association areas including the frontal cortex and the white matter, explained half of the variability in MMSE and counted for much in the cognitive impairment after stroke.

As the development of studies on the pathogenesis, the lesions on structures such as the hippocampus and entorhinal cortex which were considered to be related only to AD before have been reported to make a difference on the cognitive decline after stroke. The study conducted by Szabo *et al.* suggested that the lesion on the hippocampus could lead to the impaired persistent memory which was considered as the usual consequence of posterior cerebral artery ischemia (40). By locating the lesions with MRI, the study also showed that the infarct on the left hippocampus would impair verbal long-term memory while that on the right hippocampus may cause the nonverbal long-term memory deficits, suggesting the difference between the bilateral hippocampi. Another study on 658 elderly participants without dementia suggested that brain infarcts are associated with a smaller hippocampus, and that both infarcts and reduced hippocampal volume are independently associated with the memory decline (41). There's evidence suggesting that the impaired hippocampal neural volume is associated with the post-stroke dementia. The study has demonstrated that the vascular factors such as high cholesterol and diabetes mellitus which are related to the high stroke risk would lead to the atrophy of the hippocampus in the healthy elderly male population (42). And in the further study, Gemmell *et al.* investigated the hippocampal volume in postmortem samples and suggested that the neuronal volumes of the delayed post-stroke dementia patients were 10-20% smaller in the CA1 and CA2 hippocampal subfields, which were 20% smaller in the CA3 and CA4 hippocampal subfields, compared with elderly controls (43,44). The mechanism of hippocampus lesions

related to the post-stroke cognitive impairment remains uncertain. Li *et al.* conducted the study on middle cerebral artery occlusion model and suggested that an increased GABAergic neurotransmission which and a reduced activity of the extracellular regulated protein kinase (ERK) existed in the bilateral hippocampi and thus contributed to the cognitive impairment after ischemic stroke (45). And Wen *et al.* proposed that NaHS, the donor of the hydrogen sulfide which was a new type of neurotransmitter and inhibited the hippocampal neuronal damage, was decreased in the rats with the cognitive impairment after ischemic stroke (46). Though this attractive effect appeared on the animal model, it highlighted the role of hippocampus in the VCI and suggested a new view to the treatment of VCI.

The white matter lesions (WMLs) are the common radiological manifestations of sub-clinical ischemic damage of the cerebral parenchyma due to the small cerebrovascular disease. The lacunar stroke is frequently associated with the WMLs and caused by the ischemic damage of the small cerebrovascular disease (47). Both WML and lacunar stroke are predictors of cognitive decline and correlated to the level of cognitive impairment (47). The study on 350 elderly nondementia subjects from a community of Japan detected that the cognitive impairment which was measured by MMSE and Modified Stroop test was present in 15.7% subjects and was associated with the WMLs and remarkable cerebral atrophy (48). The Leukoaraiosis And Disability Study (LADIS) focuses on the relations between WMLs and disability in age from 65 to 84 years (49). Its branch studies provided the evidences for the relation between WMLs and VCI. One study suggested that lacunar infarcts in the thalamus were associated with lower scores of MMSE, which in the putamen/pallidum decreased the memory function (50). Another study suggested that WMLs and lacunar infarcts impaired the cognitive function, especially the psychomotor speed, executive function and global cognitive function (51). And the later study of LADIS on 477 subjects with WMLs in 3 years follow-up also showed that WMLs and brain atrophies such as medial temporal lobe atrophy, subcortical atrophy, and cortical atrophy were independently related to VCI, and the brain atrophy could accelerate the effect of WMLs on VCI (52). And the similar result was proposed by the study on 448 patients with symptomatic atherosclerotic disease from the cohort of SMART-MR in 4 years follow-up, which suggested that the interaction between brain atrophy and WMLs or infarcts could aggravate the cognitive decline (53). The pathogenesis of WMLs in VCI is unclear. The study on 32 nonstroke and

nondementia subjects with and without WMLs which were determined by the white matter hyperintensities on MRI explored the mechanism of WMLs resulting in cognitive impairment, and suggested that WMLs may lead to cortical thinning and thus impaired the executive function and verbal fluency (54).

Cerebral microbleeds (CMBs)

CMB is defined as the hemorrhage smaller than 5 mm, which could be detected by the gradient-echo T2*-weighted MRI, and has been recognized as the marker for small vascular diseases such as the subcortical small vascular disease (associated with hypertension) and cerebral amyloid angiopathy (CAA) (55,56). According to the cohort study, the prevalence of CMBs increased with age, from 6.5% in the age 45 to 50 years old to 35.7% in the age older than 80 (57). In the population of stroke survivors, about 35% patients with ischemic stroke and 60% patients with hemorrhage stroke have the CMB (58). The small vascular disease has been reported to be related to the cognitive deficits (59), especially the CAA (60). Thus the role of CMB in the cognitive impairment after stroke has been drawn much attention.

There's evidence suggesting that CMBs are related to the cognitive impairment. The study conducted by Werring *et al.* firstly suggested the relation between CMBs and cognitive deficits (61). The patients with CMBs showed an impaired executive dysfunction more frequently than those without CMBs. And the further study has suggested that the CMBs are associated with frontal-executive impairment at follow-up after 5.7 years (62). The existence of CMB may also predict the consequence of the cognitive impairment. The convincing evidences come from two large sample analyses. The AGES-Reykjavik study which included 3,906 older subjects with CMBs suggested that the multiple CMBs located in the deep locations are associated with the lower cognitive function such as slower processing speed and poorer executive function and have a high risk for the vascular dementia (63). And the Rotterdam Scan study which included 3,979 subjects without dementia as measured by the MMSE and neuropsychological batteries suggested that the presence of numerous CMBs especially in a strictly lobar location may be associated with worse performance on cognitive tests in almost all cognitive domains except memory (64).

Furthermore, one study suggested that the absence of the CMBs would contribute to the reversion of the mild VCI to normal cognitive status (65). There's evidence

suggesting that the CMBs may also have effects on the subcortical vascular dementia (66). The patients with CMBs showed the lower total MMSE score and the sub-scores in terms of "attention and calculation" and "orientation" than those without CMBs. It seems that there's a difference of the impaired cognitive domain between the locations of the CMBs. This idea is supported by the prospective studies. The study on the 439 subjects from the PROSPER study proposed that the infratentorial CMBs may be related to the impaired delayed memory (67). And the study proceeding on 500 nondemented individuals in the RUN-DMC study suggested that the presence and number of the frontal and temporal CMBs were related to the declined cognitive performance as measured by MMSE (68).

Mixed AD with stroke

AD is the most common form of the dementias, which is responsible for about 50-70% of the total demented cases (69) and surpasses the vascular dementia which is the secondary common form and constitutes 15-25% (70). A considerable overlap exists between AD and VCI. According to international working group (IWG) for new research criteria for the diagnosis of AD, the IWG-2 criteria, besides the existence of clinical and biomarker evidences of AD, the mixed AD with stroke should also include the stroke history, or focal neurological features supported by neuroimaging evidences, or both (71). The proportion of patients who suffer from AD with stroke is 56% of all demented cases (6). The CAA, which is a common cause of the stroke especially the hemorrhage stroke, is found in about 90% cases of AD (60,72). Caused by the amyloid deposition on the cerebral vessels, CAA is considered to be related to the pathogenesis of AD (73). Benedictus *et al.* suggested that the more CMBs may be associated with the higher amyloid burden, which could lead to the CAA (74). And other studies showed that CMBs may have effects on the cognitive decline in the AD patients (75,76). What's more, the atherosclerosis is also one of the common causes of stroke. The study conducted by Honig *et al.* suggested that the atherosclerosis may also have effects on the pathogenesis of AD. It showed that the neuritic plaque which was one of the main pathologic manifestations of AD increased as the aggravation of atherosclerosis (77), suggesting the inner correlation between stroke and AD.

Besides that, the risk gene of AD, APOE ϵ 4, is related to the poor cognitive outcome after stroke (78). APOE is a glycoprotein responsible for lipid transport in the brain

and circulation, including APOE2, -E3, and -E4 which are encoded by three allele genes $\epsilon 2$, $\epsilon 3$, $\epsilon 4$ on chromosome 19 (79). And APOE $\epsilon 4$ allele is widely recognized as a significant genetic risk factor for sporadic AD (80). The study has shown that the presence of the APOE $\epsilon 4$ allele is associated with the amyloid deposition in the form of neuritic plaques and the increased risk of CAA (81). Moreover, a prospective cohort study on 3,424 elderly individuals suggested that the APOE $\epsilon 4$ carriers had a higher risk of the vascular dementia than the non-carriers (82). The carriers with one $\epsilon 4$ allele had an approximately 1.6-fold greater risk of the vascular dementia, whereas those with two $\epsilon 4$ alleles had a 4.4-fold greater risk. These evidences have shown that the APOE $\epsilon 4$ is associated with the risk of both AD and VCI, and provide a promising genetic therapy target for the cognitive impairment after stroke.

Management

Treatment for cognitive impairment

So far, there's no unequivocally efficacious treatment to the post-stroke cognitive impairment. Some used in AD have shown some positive effects on post-stroke cognitive impairment. Although studies show that these drugs could make the significant improvement on some cognitive domains like executive function, the uncertainty on the global and daily function makes it difficult to evaluate the worth of the drugs on clinic (30). However, as the possible treatments of post-stroke cognitive impairment, the achievements on trials are still promising.

Cholinesterase inhibitors

Cholinesterase inhibitors, donepezil, galantamine, and rivastigmine have been approved for clinical use in AD (83). Followed by the development of the clinical trials, the cholinesterase inhibitor is confirmed as the promising drug for the treatment of the post-stroke cognitive impairment, among which the donepezil is the most promising one. The studies have suggested a significant for improving the cognitive function and daily living. The double-blind, placebo-controlled, randomized clinical trials lasting 24 weeks have suggested that the donepezil has benefits in the cognition, but inconsistent benefits in global cognitive function of the patients with post stroke cognitive impairment (84-87). The recommendation for drug treatments of VCI from American Heart Association/American Stroke Association (AHA/ASA) suggested that

donepezil could be effective for cognitive enhancement in patients with VCI and be recommended with the Class IIa; Level A evidence (30). What's more, one recent trial on patients with right hemisphere stroke who were treated with the donepezil in 4 weeks showed that the significant cognitive improvement existed as measured by MMSE and the increased activation appeared in both prefrontal areas, both inferior frontal lobes, and in the left inferior parietal lobe, which suggested that the effect of donepezil may correlated to the parieto-frontal network in the cognitive impairment after stroke (88). However, the study on the cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) patients who suffered from the subcortical ischemic vascular dementia showed different results (89). The study tested the effect of donepezil on 168 patients with CADASIL which was measured by vascular ADAS-Cog at 18 weeks. The results revealed that there was no significant difference in the vascular ADAS-cog score between the patients treated with donepezil and controls but an increased executive function existed.

Besides the donepezil, AHA/ASA also proposed the effect of other cholinesterase inhibitors such as galantamine and rivastigmine. One randomized clinical trial on galantamine suggested a significant less decline in cognition, function, and behavior in the patients with vascular dementia mixed with AD (85), while another one suggested that the galantamine could attenuate the cognitive impairment on executive function, but not on daily functions in a sample of patients with VCI (90). However, the meta-analysis on two trails failed to show the efficacy of galantamine but suggested the a higher risk of adverse gastrointestinal side-effects (91). And the trials on rivastigmine suggested the effect on executive function in VCI (92,93).

Memantine

The memantine, a noncompetitive N-methyl-D-aspartate receptor antagonist, which performs the neuroprotective effect by reducing the excitotoxicity, may have effects on both AD and VCI (94). Two randomized clinical trials have shown the memantine improves the cognition as measured by ADAS-cog and behavior as measured by NOSGER disturbed behavior, but not global functioning in patients with mild to moderate vascular dementia (95,96). However, the meta-analysis on the two trials above suggested that the benefits in cognition and behavior were not supported by clinical global measures (97). Interestingly, the effort of the

memantine test on animal model is promising. The studies *in vivo* suggested that memantine could relieve the impaired memory and decrease the neural lesions caused by cerebral ischemia (98-100). The further study on rats with cortex occlusions suggested that the treatment with memantine could reduce the growth of microinfarct and diminish the cognitive deficits (101). Although the benefit of memantine on post-stroke cognitive impairment is still uncertain (30), due to the positive effort on animal models, there's a good prospect for the future study.

Management of cerebrovascular disease

Treatment on brain lesions

As the post-stroke cognitive impairment is attributed to cerebral lesions due to stroke, it seems that the relief of cerebral lesions could contribute to the cognitive improvement. The citicoline, which is the generic name of cytidine-5'-diphosphocholine (CDP-choline, CDPCho), is widely used for the neuroprotection on clinic (102). The recent studies have shown that the citicoline could prevent the cognitive decline after stroke (103). Two clinic trials were conducted recently. The IDEALE study examined the effectiveness and safety of citicoline on patients with vascular mild cognitive impairment and suggested that the citicoline could improve the post-stroke cognition compared with controls as measured by MMSE after 9-month treatment, but failed to improve the activities of daily living (104). And the other one focused on the effect of citicoline on neurocognitive domains (105). After 12-month treatment, the stroke patients treated with citicoline showed a better functional outcome without statistically significant differences, but the cognitive functions such as the attention-executive functions and temporal orientation in citicoline group was significantly improved compared with controls. Both of the trials proposed that citicoline was a promising agent to improve the impaired cognition after stroke. Ginkgo Biloba, which is a traditional natural herbal product, plays extensive roles on the neural dysfunctions such as the impaired memory, concentration problems, dizziness, headache and so on (106). The study on the vascular dementia rat model has shown the bilobalide which is a extract from Ginkgo Biloba, could protect the learning and memory function by reducing free radical injury and inhibiting the apoptosis of neurons in the brain cortex and hippocampal CA1 region (107). And the recent meta-analyses on the clinical trials of Ginkgo Biloba for dementia suggested a change in cognitive scores

in favor of extracts of Ginkgo Biloba compared to placebo (108,109). The clinical trial on the 333 patients with AD and 71 patients with vascular dementia from the GOTADAY study suggested the EGb 761, the extract of Ginkgo Biloba, could improve the cognitive functions and activities of daily living in both AD and vascular dementia groups after 24-week treatment (110). The more recent study on patients with VCI of no-dementia suggested 3-month treatment of Ginkgo Biloba could improve the cognitive function as measured by MoCA scores and the cerebral blood flow (111).

Prevention of vascular risk factors

The increasing evidences demonstrate that the vascular risk factor related to stroke could decrease the risk of post stroke cognitive impairment. The hypertension has been confirmed to be the potential risk factor of post-stroke cognitive impairment. The meta-analysis based on 11 studies suggested that hypertension is a significant risk factor for vascular dementia in the absence of an age difference (112). The study showed that the antihypertensive treatment could reduce the risk of both the stroke and the cognitive impairment, which crossed as a basis for aggregation (113). And a population-based cohort study on 6,249 participants suggested that the use of antihypertensive drug could decrease the risk of dementia with 8% per year of use for people ≤ 75 years of age (114). The further study revealed that the effects of antihypertensive drugs on vascular dementia varied for the classes of antihypertensive drugs (115). Besides the hypertension, the other vascular risk factors such as diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation, smoking and so on, which have effects on the stroke, could also be the therapy target of post-stroke cognitive impairment (35). The study on 2,932 participants from Coronary Artery Risk Development in Young Adults study suggested that keeping weight, healthful diet, nonsmoking, physical activity, and controlling cholesterol, blood pressure, and fasting glucose were related to the better performance on cognition in later life (116).

Conclusions

The prevalence of post-stroke cognitive impairment in stroke survivors is high and varies for the difference between the countries, the races, and the diagnostic criteria. Both the demographic factors like age, education and occupation and vascular factors count for the high risk of post-stroke cognitive impairment. Post-stroke cognitive

impairment could be induced by mechanisms including the VCI due to the neuroanatomical lesions on strategic areas and the CMBs as a result of the small cerebrovascular diseases and mixed AD with stroke. The risk gene APOE $\epsilon 4$ is associated with both AD and VCI. General strategies for managing patients with have been developed. Post-stroke cognitive impairment doesn't only benefit in the application of anti-dementia treatments, but also the measures focusing on cerebrovascular diseases. Due to the conflictive results of the clinical studies, the further studies still need to determine the efficacy of various therapy strategies.

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